FORMULATION AND DEVELOPMENT OF FIXED DOSE COMBINATION OF ARTEMETHER AND LUMEFANTRINE TABLETS FOR THE TREATMENT OF MALARIA

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

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In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by
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Under the guidance of

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All India Council for Technical Education. New Delhi.

CERTIFICATE

This is to certify that **Reg. No: 26111014** carried out the dissertation work on **"FORMULATION AND DEVELOPMENT OF FIXED DOSE COMBINATION OF ARTEMETHER AND LUMEFANTRINE TABLETS FOR THE TREATMENT OF MALARIA"** for the award of degree of **MASTER OF PHARMACY IN PHARMACEUTICS** of **THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY, CHENNAI** and is bonafide record work done under my Supervision and Guidance in the Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-600 097 during the academic year 2012-2013.

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I wish her success in all her future endeavours.

For Medopharm Pvt. Ltd.

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DECLARATION

I do hereby declare that the thesis entitled **"FORMULATION AND DEVELOPMENT OF FIXED DOSE COMBINATION OF ARTEMETHER AND LUMEFANTRINE TABLETS FOR THE TREATMENT OF MALARIA"** by **Reg. No: 26111014** submitted in partial fulfillment for degree of **Master of Pharmacy in Pharmaceutics** was carried under the guidance and supervision of **Dr. U.UBAIDULLA M. Pharm., Ph.D., (**Institutional guide) and **Mr. Jayanta Kumar Bhuyan (**Industrial guide) during the academic year 2012-2013. The work embodied in this thesis is original, and is not submitted in part or full for any other degree of this or any other University.

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(Reg.No: 26111014)

ABBREVIATIONS

API	Active pharmaceutical Ingredient
HCL	Hydrochloric Acid
HPLC	High performance liquid chromatography
FTIR	Fourier transformer infrared spectroscopy
IPA	Iso Propyl Alcohol
IR	Infrared spectroscopy
MCC	Micro crystalline cellulose
ACT	Artemisinin based Combination Therapy
UV	Ultraviolet
ICH	International Conference on Harmonization
Int.Ph.	International Pharmacopoeia
RH	Relative Humidity
USP	United States Pharmacopoeia
IP	Indian Pharmacopoeia
CI	Compressibility Index
HR	Hausner's Ratio
WHO	World Health Organisation
RSD	Relative Standard Deviation
A	Artemether
L	Lumefantrine
CCS	Croscarmellose Sodium

NOMENCLATURE

%	Percentage
µg/ml	Microgram/millilitre
Conc	Concentration
gm/cc	Gram/cubic centimetre
Hr	Hour
Kg/cm2	Kilogram/square centimetre
Min	Minute
Mm	Millimetre
Ng	Nanogram
ng/ml	Nanogram/millilitre
ng-hr/ml	Nanogram-hour/millilitre
Nm	Nanometer
SD	Standard Deviation
Sec	Seconds

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1. INTRODUCTION

Pharmaceutical formulation, in pharmaceutics, is the process in which different chemical substances, including the active drug, are combined to produce a final medicinal product.

Formulation studies involve developing a preparation of the drug which is both stable and acceptable to the patient. For orally taken drugs, this usually involves incorporating the drug into a tablet or a capsule. It is important to appreciate that a tablet contains a variety of other substances apart from the drug itself, and studies have to be carried out to ensure that the drug is compatible with these other substances.

A tablet is usually a compressed preparation that contains:

- 5-10% of the drug (active substance);
- 80% of fillers, disintegrants, lubricants, glidants, and binders; and
- 10% of compounds which ensure easy disintegration, disaggregation, and dissolution of the tablet in the stomach or the intestine.

Fixed-dose combinations (FDCs)[1]

The development of fixed-dose combinations (FDCs) is becoming increasingly important from a public health perspective. Such combinations of drugs are being used in the treatment of a wide range of conditions and are particularly useful in the management of HIV/AIDS, **malaria** and tuberculosis, which are considered to be the foremost infectious disease threats in the world today.

Definition

A **combination drug** or **fixed-dose combination** (**FDC**) is a formulation of two or more active ingredients combined in a single dosage form, available in certain fixed doses. When the drug product is a "pill" (e.g., tablet or capsule for oral consumption) the FDC product can also be called a "polypill."

Recently, in India Fixed Dose Combination (FDC) of Drugs / medicines has drawn the attention of health service providers and the service recipients. A fixed dose combination (FDC) is a formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses. Fixed dose combination drug products may improve medication compliance of patients. Fixed dose combination drugs are also developed to target a single disease like AIDS, TB and malaria. Some of the FDCs are reviewed by the FDA and the active ingredients used therein are not expected to interact adversely with each other, but may interact with other drugs that a patient is taking. Though FDCs may reduce burden of consuming more pills, there are some disadvantages. Like, if a patient needs dosage adjustment, the existing FDC may not suit the most appropriate strength for the patient. Further, after using an FDC if an adverse drug reaction occurs, it may be difficult to identify the active ingredient responsible for causing the reaction. A pharmaceutical company may develop a FDC with the sole aim of marketing advantage of exclusive rights to sell the FDC, even though the individual active ingredients may be off-patent. When more than two drugs are combined, the cumulative toxicity and risk-benefits of the new product need to be examined before marketing such products.

FDC & Infectious Diseases

There is emergence of previously unreported infectious diseases and re-emergence of infectious diseases thought to be on the way to elimination. There is also evidence of infectious pathogens exhibiting antimicrobial resistance even in multiple-drug usage.

Advantages and disadvantages of fixed-dose combinations

Advantages

- Simpler dosage schedule improves compliance and therefore improves treatment outcomes

- Reduces inadvertent medication errors Prevents and/or slows attainment of antimicrobial resistance by eliminating monotherapy (i.e, one drug is never by itself in circulation)
- Allows for synergistic combinations (i.e., trimethoprim / sulfamethoxazole combination allows each drug to selectively interfere with successive steps in bacterial folate metabolisms
- Eliminates drug shortages by simplifying drug storage and handling, and thus lowers risk of being "out of stock"
- Only 1 expiry date simplifies dosing (single products may have different expiry dates)
- Procurement, management and handling of drugs is simplified
- Lower packing and shipping costs
- Less expensive than single ingredient drugs
- Side effects are reduced by using one drug of the combination for this purpose
- Potential for drug abuse can be minimized by using one drug of the combination for this purpose (i.e., excessive use of the antidiarrheals).

Disadvantages

- FDCs are (possibly) more expensive than separate tablets
- Potential quality problems, especially with rifampicin in FDCs for TB, requiring bio-availability testing
- If a patient is allergic or has a side-effect to 1 component, the FDC must be stopped and replaced by separate tablets
- Dosing is inflexible and cannot be regulated to patient's needs (each patient has unique characteristics such as weight, age, pharmacogenetics, co-morbidity, that may alter drug metabolism and effect).
- Incompatible pharmacokinetics is irrational because of different elimination ½ lives of individual components
- Reaction of one of the components (e.g., a rash to sulfamethoxazole in cotrimoxazole) may result in patient avoiding the "innocent" trimethoprim in the future

- Drug interactions may lead to alteration of the therapeutic effect.
- Combinations make therapeutic sense for HIV, TB and malaria, but the evidence for the utility of combinations is still largely circumstantial.
- The products should have therapeutic rationale and are safe, to remain in the market. Poly-pills are used in the UK for primary prevention of heart diseases. Multiple components of FDCs can lead to complex issues of IPR access and global IP rules.

Tablets:[6,7]

Tablets are solid oral dosage forms usually prepared with the aid of suitable pharmaceutical excipients. They may vary in size, shape, weight, hardness, thickness, disintegration, dissolution characteristics and in other aspects, depending on their intended use and method of manufactures.

1.1. ADVANTAGES[16]

Tablets are simple and convenient to use. They provide an accurately measured dosage of the active ingredient in a convenient portable package, and can be designed to protect unstable medications or disguise unpalatable ingredients.

- Colored coatings, embossed markings and printing can be used to aid tablet recognition. Manufacturing processes and techniques can provide tablets special properties, for example, sustained release or fast dissolving formulations.
- Noninvasive
- Portability
- Hard to tamper with tablets
- Easy to swallow, especially if coated.
- Relatively easy to manufacture and package
- Provide accurate dosing
- Increased stability of the drug when compared to liquid dosage forms.
- Product identification is easy especially with use of imprints.

- Can be enteric coated or designed for delayed release.
- Offers greatest capability of all oral dosage forms for the greatest dosage precision & least content Uniformity.
- High patient compliance.
- Their cost is lowest of all dosage forms
- One of the major advantages of tablet over capsules is that the tablet is essentially "tamperproof dosage form".
- Easiest and cheapest to packaging and shipment
- They are having best combined properties of chemical, mechanical and microbiological properties
- Accuracy of dose is maintained since tablet is a solid unit dosage forms
- Longer expiry period and minimum microbial spillage owing to lower moisture content
- Large scale manufacturing is feasible in comparison to other dosage forms. Therefore, economy can be achieved.
- Organoleptic properties (taste, appearance, and odor) are improved by coating of the tablets. Product identification is easy and marketing done with the help of grooved punches and printing with edible ink.
- As a tablet is not a sterile dosage form, stringent environmental conditions are not required in the tablet department.

1.2. DISADVANTAGES

- Drugs with poor wetting, slow dissolution property, large dosages or any combination of these features may be difficult or impossible to formulate & manufacture as a tablet.
- It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
- Slow onset of action as compared to parenterals, liquid orals and capsules.

CLASSIFICATION OF TABLETS

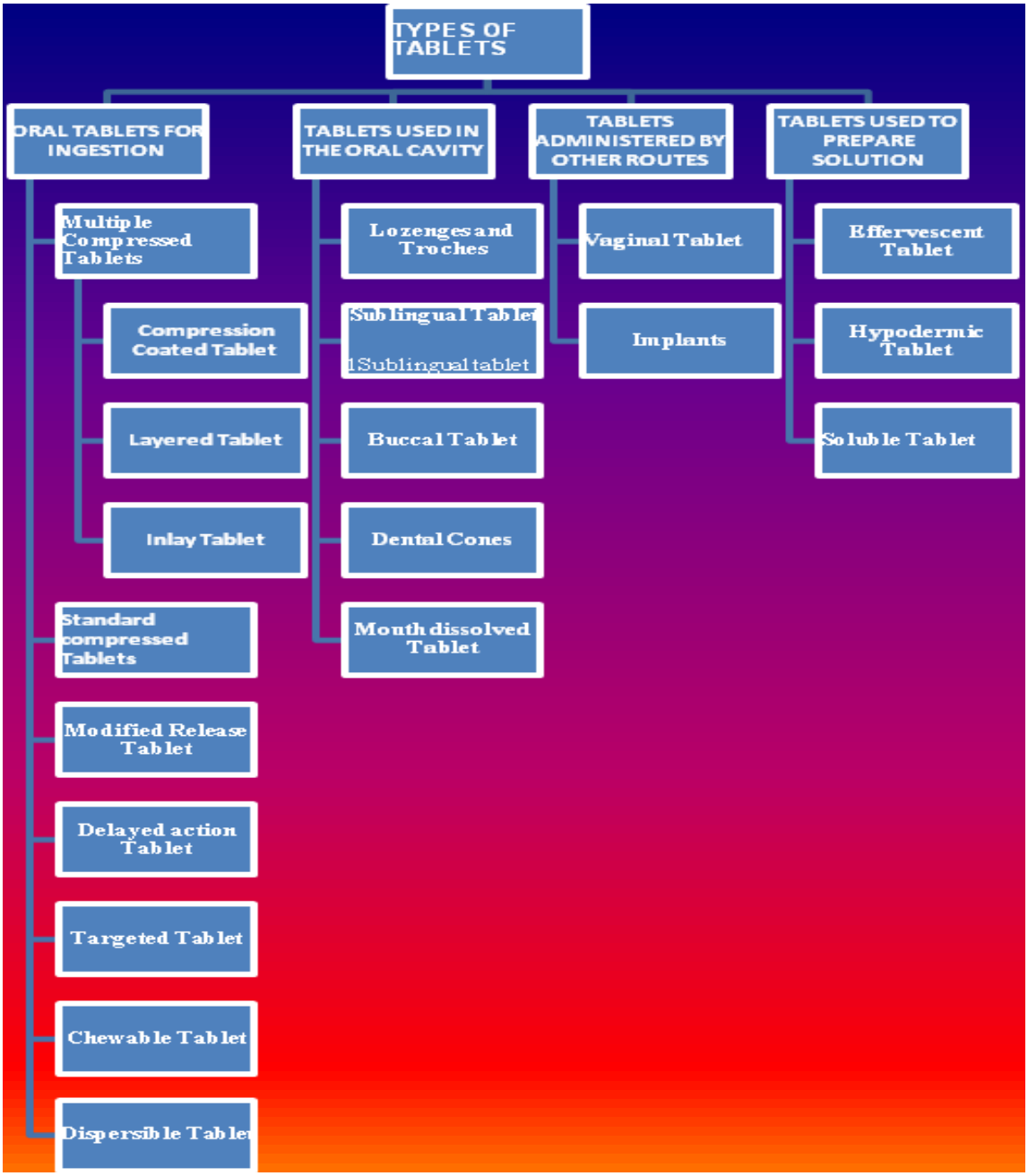


Fig No.1

1.3. TYPES AND CLASSES OF TABLETS:[8,14,17,18]

Tablets are classified by their route of administration or function, by the type of drug delivery system they represent within that route, by their form and method of manufacture.

1.3.1. Tablets ingested orally:

Compressed tablets:

These tablets are uncoated and made by compression of granules. These tablets are usually intended to provide rapid disintegration and drug release. These tablets contain water-soluble drugs, which after swallowing get disintegrated in the stomach, and its drug contents are absorbed in the gastrointestinal tract and distribute in the whole body.

Multiple compressed tablets:

These tablets are prepared to separate physically or chemically incompatible ingredients or to produce repeat action prolonged action products. To avoid incompatibility, the ingredients of the formulation except the incompatible materials are compressed into a tablet then incompatible substance along with necessary excipients are compressed tablet.

Multilayered tablets:

These tablets consist of two or more layer of materials compressed successively in the same tablets. The color of each layer may be the same or different. The tablets having layers of different colours are known as "multicoloured tablets".

Sustained action tablets:

These tablets are used to get a sustained action of medicament. These tablets when taken orally release the medicament in a sufficient quantity as and when required maintaining the maximum effective concentration of the drug in the blood through out the period of treatment

Enteric-coated tablets:

These are compressed tablets meant for administration by swallowing and are designed to bypass the stomach and get disintegrated in the intestine only. These tablets are made to release the drug undiluted and in the highest concentration possible within the intestine. Eg: tablets containing anthelmentics, and amoebic ides.

Sugar coated tablets:

The compressed tablets having a sugar coating are called "sugar coated tablets".

Film coated tablets:

The compressed tablets having some polymer substance, such as hydroxy propyl cellulose, hydroxy propyl methylcellulose, and ethyl cellulose.

Chewable tablets:

These tablets are chewed in the mouth and broken into small pieces. In this way, the disintegration time is reduced and the rate of absorption of the medicament is increased. e.g.: aluminium hydroxide tablets, and phenolphthalein tablets.

1.3.2. Tablets used in oral cavity:

Buccal Tablets:

These tablets are to be placed in the buccal pouch or between the gums and lips or cheek where they dissolve or disintegrate slowly and are absorbed directly without passing into the alimentary canal. Eg: tablets of ethisterone.

Sublingual tablets:

These tablets are to be placed under the tongue where they dissolve or disintegrate quickly and are absorbed directly without passing into GIT.

Eg: tablets of glyceryl trinities.

Lozenge and Torches:

These tablets are designed to external local effect in the mouth or throat. These tablets are commonly used to treat sore throat or to control coughing in common cold. They may contain local anaesthetics antiseptic, antibacterial agents, astringent and antitussives.

1.3.3. Tablets used to prepare solution:

Effervescent tablets:

In addition to the drug substance, these contain sodium bicarbonate and an organic acid such as tartaric acid or citric. In the presence of water, these additives react, liberating carbon dioxide that acts as disintegrator and produces effervescence. Except for small quantities of lubricants present, effervescent tablets are soluble. Tablet triturates usually are made from moist material, using a triturate mild that gives them the shape of cut sections of cylinder. Such tablets must be completely and rapidly soluble; the problem arising from the compression of these tablets is the failure to find a lubricant that is completely water-soluble.

Dispensing tablets:

These tablets provide a convenient quality of potent drug that can be incorporated readily in to powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are. Supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.

Hypodermic tablets:

Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. Since stable parenteral solutions are now available for most new drug substances, there is no justification for the hypodermic tablets for injection. Their use in this manner should be discouraged, since the resulting solutions are not sterile. Large quantities of these tablets continue to be made, but for oral administration. No hypodermic tablets ever have been recognized by the official compendia

1.3.4. Inserted Tablets:

Dental cones:

These are relatively minor compressed tablets meant for placing them in the empty socket-after tooth extraction. They prevent the multiplication of bacteria in the socket following such extraction by using slow releasing antibacterial compounds or to reduce bleeding by containing the astringent. These cones generally get dissolved in 20 to 40 min time.

Implantation tablets:

These tablets are placed under the skin or inserted subcutaneous by means of minor surgical operation and are slowly absorbed. These implants must be sterile and should be packed individually in sterile condition. Implants are mainly used for administration of hormones such as testosterone, and deoxycorticosterone etc.

Vaginal tablets:

These tablets are meant to dissolve slowly in the vaginal cavity. These tablets are typically ovoid or pear shaped to facilitate retention in the vagina. This tablet form is used to release steroids, antibacterial agents, antiseptics or astringents to treat vaginal infections.

The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration that is, the drug delivery system should delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment.

1.4. EXCIPIENTS USED IN THE FORMULATION[11,12]

A compressed tablet usually consists of active medicaments mixed with a number of inert substances known as "excipients or additives". These additives are added to give the better quality to a tablet. Although these additives are termed as inert but they have a great influence on stability, bioavailability and the process by which the dosage forms are prepared.

1.4.1. Excipients and their functionalities:

Excipient means any component other than the active pharmaceutical ingredient(s) intentionally added to the formulation of a dosage form. Excipients are chosen in tablet formulation to perform a variety of functions like

- For providing essential manufacturing technology functions [binders, glidants, lubricants]
- For enhancing patient acceptance [flavors, colourants]
- For providing aid in product identification [colourants]
- For optimizing or modifying drug release [disintegrants, hydrophilic polymers, wetting agents, biodegradable polymers]
- For enhancing stability [antioxidant, UV absorbers]

1.4.2. Disintegrants:[19,28]

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The drugs solubility mainly depends on physical – chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet.

The drug will dissolve at a slower rate from a non-disintegrating tablet due to exposure of limited surface area to the fluid. The disintegration test is an official test and hence a batch of tablet must meet the stated requirements of disintegration.

Disintegrants an important excipient of the tablet formulation, is always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and the excipients which induce this process are known as disintegrants.

The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet.

Mechanism of tablet disintegrants

The tablet breaks to primary particles by one or more of the mechanisms listed below:-

- By capillary action
- By swelling
- Because of heat of wetting
- Due to disintegrating particle/particle repulsive forces
- Due to deformation
- Due to release of gases
- By enzymatic action

List of Disintegrants

Disintegrants	% Concentration in Tablets	Special comments
Starch 1500	5-15	-
Starch USP	5-20	Higher amount is required, poorly compressible

Avicel® (PH 101, PH 102)	10-20	Lubricant properties and directly compressible
Solka floc®	5-15	Purified wood cellulose
Alginic acid	1-5	Acts by swelling
Sodium alginate	2.5-10	Acts by swelling
Explotab®	2-8	Sodium starch glycolate, super disintegrant.
Polyplasdone®(XL)	0.5-5	Crosslinked PVP
Amberlite® (IPR 88)	0.5-5	Ion exchange resin
Methyl cellulose, Sodium CMC, HPMC	5-10	-
AC-Di-Sol®	1-3	Direct compression
Carbon dioxide	_	Created insitu in effervescent tablet

Table No.1

1.4.3. SUPERDISINTEGRANTS:[20,30]

As days passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs.

And this superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

List of Super Disintegrants

Super Disintegrants	Mechanism of action	Special comment
Crosslinked cellulose	- Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Crosslinked starch	-Swells 7-12 folds in <30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Natural super disintegrant	--	-Does not contain any starch or sugar. Used in nutritional products.
Calcium silicate	-Wicking action	-Highly porous, -light weight -optimum concentration is between 20-40%

Table No.2

1.4.4. Diluents:

In order to facilitate tablet handling during manufacture and to achieve targeted content uniformity, the tablet size should be kept above 2-3 mm and weight of tablet above 50 mg. Many potent drugs have low dose (for e.g. Diazepam, Clonidine

hydrochloride). In such cases diluents provide the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size. Usually the range of diluents may vary from 5-80%. Diluents are also synonymously known as "fillers". Diluents are often added to tablet formulations for secondary reasons like to provide better tablet properties such as:

i) To provide improved cohesion
ii) To allow direct compression manufacturing
iii) To enhance flow
iv) To adjust weight of tablet as per die capacity

Classification of diluents:[26]

Tablet diluents or fillers can be divided into following categories:

i) Organic Materials - Carbohydrate and modified carbohydrates.
ii) Inorganic Materials – Calcium phosphates and others.
iii) Co-processed Diluents.

Carbohydrate substances such as sugars, starches and celluloses may also function as binders during wet granulation process. Whereas when used in direct compression system, they serve as the diluents. The inorganic diluents do not exhibit binding properties when used in wet granulation and direct compression.

Tablet diluents or filler may also be classified on the basis of their solubility in water.

List of Diluents/fillers

Insoluble tablet fillers or diluents	Soluble tablet fillers or diluents
Starch	Lactose
Powdered cellulose	Sucrose
Microcrystalline cellulose	Mannitol
Calcium phosphates, etc.	Sorbitol, etc.

Table No.3

Selection of diluent should be done after considering the properties of diluent such as: Compactibility, flowability, solubility, disintegration qualities, hygroscopicity, lubricity and stability.

1.4.5. Binders:

Binders are added in tablet formulation to have required flow property and compressibility of powders.

List of Binders

Sugars	Natural binders	Synthetic/Semi synthetic Polymer
Sucrose	Acacia	Methyl Cellulose
Liquid glucose	Tragacanth	Ethyl Cellulose
	Gelatin	Hydroxy Propyl Methyl Cellulose (HPMC)
	Starch Paste	Hydroxy Propyl Cellulose
	Pregelatinized Starch	Sodium Carboxy Methyl Cellulose
	Alginic Acid	Polyvinyl Pyrrolidone (PVP)
	Cellulose	Polyethylene Glycol (PEG)
		Polyvinyl Alcohols
		Polymethacrylates

Table No.4

1.4.6. Glidants:

Guidant's are added to the formulation to improve the flow properties of the material which is to be fed into the die cavity and aid in particle rearrangement within the die during the early stages of compression. If the flow properties are extremely poor then glidants are ineffective and consideration of force free mechanisms may be necessary. Starch is a popular glidant because it has additional value of disintegrant. Concentration of starch is common up to 10%, but should be limited otherwise it will worsen the flow of material. Talc is a glidant which is superior to starch but its concentration should be limited because it has retardant effect on dissolution-disintegration profile. Silaceous material like colloidal silica i.e. syloid, pyrogenic

silica (0.25%), hydrated sodium silioaluminate (0.75%) are also successfully used to induce flow.

Glidants act by interposing their particles between those of material and lower the overall interparticulate friction of the system by virtue of their reduced adhesive tendencies. Similar to lubricants, they are required at the surface of feed particles and they should be in fine state of division and appropriately incorporated in the mixture.

1.4.7. Anti-adherents:

Some material have strong adhesive properties towards the metal of punches and dies and also the tablet formulation containing excessive moisture which has tendency to result in picking and sticking problem. Therefore antiadherents are added, which prevent sticking to punches and die walls. Talc, magnesium stearate and corn starch have excellent antiadherent properties. Silicon oil can also be used as antiadherent.

List of anti adherents

Anti adherent	% Concentration	Comment
Talc	1 – 5	Lubricant with excellent antiadherents properties
Cornstarch	3 – 10	Lubricant with excellent antiadherents properties
Colloidal silica	0.1 – 0.5	Does not give satisfactory results due to small surface area. Cab-O-Sil® and Syloid®
DL-Leucine	3 – 10	Water soluble lubricant; excellent antiadherents properties
Sodium lauryl sulphate	<1	Antiadherents with water soluble lubricant
Stearates	<1	Antiadherents with water insoluble lubricant

Table No.5

1.4.8. Lubricants

Lubricants are the agents that reduce friction by interposing an intermediate layer between the tablet constituents and the die wall during compression and ejection. Solid lubricants act by boundary mechanism which results from the adherence of the polar portions of molecules with long carbon chains to the metal surfaces to the die wall. Magnesium stearate is an example of boundary lubricant. Other process is hydrodynamic mechanism i.e. fluid lubrication where two moving surfaces are separated by a finite and continuous layer of fluid lubricant. Since adherence of solid lubricants on the die wall is more than that of fluid lubricants, solid lubricants are more effective and more frequently used.

Classification of lubricants:

Lubricans are classified according to their water solubility i.e. water insoluble and water soluble. Selection of lubricant depends partly on mode of administration, type of tablet, desired disintegration and dissolution properties, physicochemical properties of granules or powder and the cost.

I. Water insoluble lubricants:

Water insoluble lubricants are most effective and used at low concentration than water soluble lubricants. Since these lubricants function by coating , their effectiveness is related with their surface area, extent of particle size reduction, time, procedure of addition and length of mixing.

List of insoluble lubricants

Insoluble lubricants	%Concentration	Comments
Stearates (Magnesium Stearate, Calcium Stearate, Sodium stearate)	0.25 -1	Reduce tablet strength; prolong disintegration; widely used.
Talc	1 -2	Insoluble but not hydrophobic; moderately effective.
Sterotex	0.25 – 1	-

Waxes	1 – 5	-
Stearowet	1 – 5	-
Glycerylbehapate (Compritol®888)	1 – 5	Both lubricant and binder;
Liquid paraffin	Up to 5	Dispersion problem; inferior to stearates

Table No.6

II. Water soluble lubricants:

Water soluble lubricants are used when a tablet is completely soluble or when unique disintegration and dissolution characteristics are required. Tablet containing soluble lubricant shows higher dissolution rate than tablet with insoluble lubricants. Physical mixture of this lubricants i.e. SLS or MLS with stearates can lead to the best compromise in terms of lubricity, tablet strength and disintegration.

List of soluble lubricants

Water soluble lubricants	% Concentration
Boric acid	1
Sodium benzoate	5
Sodium oleate	5
Sodium acetate	5
Sodium Lauryl Sulfate (SLS)	1 – 5
Magnesium Lauryl Sulfate (MLS)	1 – 2

Table No.7

1.5. MANUFACTURING METHOD[9]

There are four general methods of tablet preparation.

- Direct compression
- Wet granulation method
- Dry granulation method
- Fluidized bed granulation

In the tablet-pressing process, it is important that all ingredients be dry, powdered, and of uniform grain size as much as possible. The main guideline in manufacture is to ensure that the appropriate amount of active ingredient is equal in each tablet so ingredients should be well-mixed. Compressed tablets are exerted to great pressure in order to compact the material. If a sufficiently homogenous mix of the components cannot be obtained with simple mixing, the ingredients must be granulated prior to compression to assure an even distribution of the active compound in the final tablet. Two basic techniques are used to prepare powders for granulation into a tablet: wet granulation and dry granulation. Powders that can be mixed well do not require granulation and can be compressed into tablets through Direct Compression.

1.5.1. Direct Compression Method:[15]

Direct compression method does not involve any addition of fluid before the compression of the tablets. This method should be the first choice of any tablet formulation because of its uncomplicated manufacturability and cost effectiveness. Other advantages of this technique are getting the drug product with less disintegration time and faster dissolution rate, better stability of an API in a drug product due to less processing steps and a good choice for moisture sensitive drug.

A tablet can be made by direct compression method in the following way,

- Sift an API, diluent /diluents, binder, disintegrant, lubricant, others separately through sieves of an appropriate pore size.
- Transfer the above mixer except lubricant in a blender of appropriate capacity. Note that the occupancy in the blender should be at least 30 % to the maximum of 70 % of total capacity. More occupancy will lead to improper mixing whereas very less occupancy will lead to segregation of materials.
- For higher dose drugs normally 10 to 15 minutes of mixing is sufficient.
- At the end of the blending process, add lubricant and mix the blend for the appropriate time. Avoid mixing lubricant for longer period of time as it may increase the hydrophobicity of the blend by coating API and other ingredients.
- For lower dose drugs, fix the blending time by gradually increasing the time of mixing say every 10 minutes. Collect the samples from five different points (four corners and one in the center) in a blender every 10 minutes. Collect the samples till 30 to 45 minutes.
- Analyze the sample for content uniformity. Choose the blending time at which you get a good content uniformity.

1.5.2. Granulation method:[21]

Granulation method is used to get the granules of uniform and equal size in order to avoid variation in filling of dies in compression machines which in turn avoids the variation in tablet weight.

Generally there are two methods of granulation adopted in industries:

1.5.2. a. Dry Granulation Technique:

By dry granulation technique, the powder mixture is compacted in large pieces and subsequently broken down or sized into granules. For this method, either the active ingredient or the diluents must have cohesive properties. Dry granulation is specially

applicable to materials that cannot be prepared by wet granulation because they degrade in moisture or the elevated temperature required for drying the granules.

Weigh API and other excipients along with lubricant and compact them through the roller compactor or make slugs.

Mill the compacted blend / slugs in multi-mill or quadro comil through sieve of appropriate pore size.

Mix the sieved blend with weighed quantity of lubricant in a blender for an appropriate time.

Finally compress the blend into tablets.

Note: If the materials during compaction are sticking inside the compaction machine then add some amount of lubricant with API and other excipients during compaction process itself.

1.5.2. b. Wet Granulation Technique:

Wet granulation technique involves addition of fluid to form granules. Wet granulation technique improves the flow of the powder and increases mechanical strength of the tablet. Wet granulation process is used when the drug is not very much sensitive to moisture. Wet granulation is done in rapid mixer granulator (RMG) or Fluid bed process (FBP) in industries.

I. Wet granulation using Rapid mixer granulator

For wet granulation process, weigh the required materials separately and pass them through the sieve of appropriate pore size (normally ASTM Sieve no. # 30).

Transfer the sieved materials to RMG of appropriate capacity and mix for 10 minutes at particular RPM. The RPM of the RMG should be fixed at a point when slight whirlpool is visible in the blend to ensure the mixing of the blend from top to bottom.

Add the binder solution slowly to the blend within 2 to 3 minutes. Further run the machine for 1 minute after addition of binder for the uniform distribution of fluid in the blend.

Stop the machine. Mix the blend manually with S.S. spatula or S.S. spoon. This process is known as racking. Racking is necessary to remove the materials which are stuck to the sides of RMG and caking at the bottom.

You can further run the machine for 1 to 2 minutes after racking either adding extra quantity of solvent (in case granules are not formed) or without adding extra solvent (in case granules are almost formed).

Document every action such as quantity of binder solution used, set RPM, time of addition of binder, racking, time of mixing the blend after addition of solvent, time of addition of extra solvent and quantity of extra solvent. These parameters are important for the reproducibility of the batch and understand the nature of API.

Normally binder containing 10 % w/w of solid content is preferred. The percentage of solid content can be decreased or increased based on observation of granules formation.

The amount of binder can be increased if the granules formed are softer and the amount of binder can be reduced if the granules formed are harder.

You can use aqueous solution of binder where HPMC, HPC, PVP etc. can be used as binder. Out of above mentioned binders HPMC is required to be dispersed initially in warm water as HPMC forms lumps in cold water and takes long time to dissolve.

Once the granules are formed, they are unloaded from RMG and dried in fluid bed drier or tray drier at a temperature where the drug will not degrade. Most of the drugs are stable at 60˚ C temperature. Generally the granules are dried till its LOD is less than 4 %w /w.

II. Wet granulation using Fluid bed processor[31]

Wet granulation can also be done by using fluid bed processor. Granules made in FBP are uniform, porous and small in size. Granulation process in FBP is briefly explained below:

The weighed and sieved ingredients [API and other excipients] are loaded in FBP and mixed at low blower speed for 5 minutes or more.

Set the spray RPM, atomization pressure, blower speed, inlet temperature, product temperature and exhaust temperature.

In the beginning, keep the blower speed low as the blend will be in powder form and increase in blower speed will cause the finer materials to stick to the filter bag and escape through the exhaust of FBP.

Start spraying the binder solution and observe the granulation process. Spray rate of the binder solution can be adjusted through an observation of the granulation process. Avoid lumping of granules.

At the end of granulation process dry the granules till its LOD is less that 4 % w/w.

1.5.3. Preparation of final blend:

The dried granules are passed through sieve of appropriate pore size to get uniform granules.

The sieved granules are lubricated with lubricant in a blender and finally compressed into tablets.

1.5.4. Compression Process:[15]

Compression process is the final step in tablet preparation.

- Appropriate size of punches and dies are selected and fixed in compression machine.

- Fill the blend in the hopper. Observe the flow of the blend from hopper to the turret of the compression machine.
- Initially adjust the weight of a tablet by keeping lower hardness. Once the weight is set, adjust the hardness and thickness of the tablet. Hardness and thickness are inversely proportional to each other.
- Keep checking the weight of tablets in between the compression process.
- Collect the tablets in appropriate container.
- You can install dehumidifier in the compression room for moisture sensitive products or install sodium vapour lamp for light sensitive products.

1.5.5. Minitablets:

The preparation of minitablets is similar to that of single unit tablet except the size of the granules is smaller and more uniform.

For minitablet the punch and die size will be from 1 to 3 mm in size. Smaller granule size is necessary to avoid more void spaces between granules and avoid weight variation.

Check the compression load in case of minitablets as the punches are thin and less stronger than bigger punches.

Check the weight of each minitablet in between the compression process.

Fill the Minitablets into capsules.

1.5.6. Dry granulation:

This process is used when the product needed to be granulated may be sensitive to moisture and heat. Dry granulation can be conducted on a press using slugging tooling or on a roller compactor commonly referred to as a chilsonator. Dry granulation equipment offers a wide range of pressure and roll types to attain proper densification. However, the process may require repeated compaction steps to attain

the proper granule end point. It requires drugs or excipients with cohesive properties.

- Some granular chemicals are suitable for direct compression (free flowing) e.g. potassium chloride.
- Tableting excipients with good flow characteristics and compressibility allow for direct compression of a variety of drugs.

1.5.7. Fluidized bed granulation:

It is a multiple step process performed in the same vessel to pre-heat, granulate and dry the powders. It is today a commonly used method in pharmaceuticals because it allows the individual company to more fully controls the powder preparation process. It requires only one piece of machinery that mixes all the powders and granules on a bed of air.

Unit operations involved in wet granulation, dry granulation and direct compression:

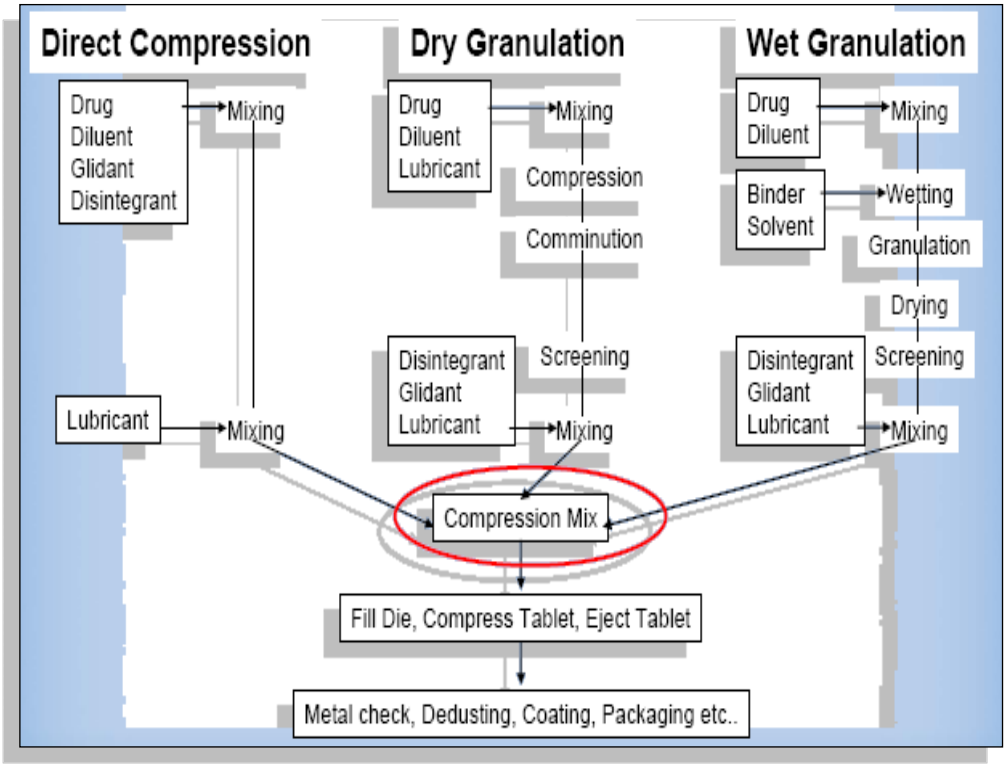


Fig. No.2

1.6 COMPRESSION

1.6.1. Introduction:

The tablet press is a high-speed mechanical device. It 'squeezes' the ingredients into the required tablet shape with extreme precision. It can make the tablet in many shapes, although they are usually round or oval. Also, it can press the name of the manufacturer or the product into the top of the tablet. Each tablet is made by pressing the granules inside a die, made up of hardened steel. The die is a disc shape with a hole cut through its centre. The powder is compressed in the centre of the die by two hardened steel punches that fit into the top and bottom of the die. The punches and dies are fixed to a turret that spins round. As it spins, the punches are driven together by two fixed cams - an upper cam and lower cam. The top of the upper punch (the punch head) sits on the upper cam edge .The bottom of the lower punch sits on the lower cam edge.

The shapes of the two cams determine the sequence of movements of the two punches. This sequence is repeated over and over because the turret is spinning round. The force exerted on the ingredients in the dies is very carefully controlled. This ensures that each tablet is perfectly formed. Because of the high speeds, they need very sophisticated lubrication systems. The lubricating oil is recycled and filtered to ensure a continuous supply.

After the preparation of granules (in case of wet granulation) or sized slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to get final product.

The compression is done either by single punch machine (stamping press) or by multi station machine (rotary press).

1.6.2. Common stages occurring during compression:

Stage 1: Top punch is withdrawn from the die by the upper cam Bottom punch is low in the die so powder falls in through the hole and fills the die.

Stage 2: Bottom punch moves up to adjust the powder weight-it raises and expels some powder.

Stage 3: Top punch is driven into the die by upper cam Bottom punch is raised by lower cam. Both punch heads pass between heavy rollers to compress the powder.

Stage 4: Top punch is withdrawn by the upper cam. Lower punch is pushed up and expels the tablet. Tablet is removed from the die surface by surface plate

Stage 5: Return to stage 1.

1.6.3. Auxiliary Equipments:

Granulation Feeding Device In many cases, speed of die table is such that the time of die under feed frame is too short to allow adequate or consistent gravity filling of die with granules, resulting in weight variation and content uniformity. These also seen with poorly flowing granules. To avoid these problems, mechanized feeder can employ to force granules into die cavity.

1.6.3.a. Tablet weight monitoring devices:

High rate of tablet output with modern press requires continuous tablet weight monitoring with electronic monitoring devices like Thomas Tablet Sentinel, Pharmakontroll and Killan control System-MC. They monitor force at each compression station by strain gage technology which is then correlated with tablet weight.

1.6.3.b. Tablet Deduster:

In almost all cases, tablets coming out of a tablet machine bear excess powder on its surface and are run through the tablet deduster to remove that excess powder.

1.6.3.c. Fette machine:

Fette machine is device that chills the compression components to allow the compression of low melting point substance such as waxes and thereby making it possible to compress product with low meting points.

1.7 Packaging

Pharmaceutical manufacturers have to pack their medicines before they can be sent out for distribution. The type of packaging will depend on the formulation of the medicine.

'Blister packs' are a common form of packaging used for a wide variety of products. They are safe and easy to use and they allow the consumer to see the contents without opening the pack. Many pharmaceutical companies use a standard size of blister pack. This saves the cost of different tools and to change the production machinery between products. Sometimes the pack may be perforated so that individual tablets can be detached. This means that the expiry date and the name of the product have to be printed on each part of the package. The blister pack itself must remain absolutely flat as it travels through the packaging processes, especially when it is inserted into a carton. This poses interesting problems for the designers. Extra ribs are added to the blister pack to improve its stiffness.

1.8 PROBLEMS IN TABLET MANUFACTURING[10,13]

An ideal tablet should be free from any functional defect or visual defect. Functional defects are due to faulty formulation. Visual defect are either related to imperfections in any one or more of the following factors:

- Tableting Process
- Excipient
- Machine

The problems in manufacturing and their remedies are

1.8.1. Lamination:

Definition:

'Lamination' is the separation of a tablet into two or more distinct horizontal layers.

Reason:

Air–entrapment during compression and subsequent release on ejection.The condition is exaggerated by higher speed of turret.

The causes and remedies of lamination related to 'formulation' (Granulation)

S.No.	Causes	Remedies
1.	Oily or waxy materials in granules	Modify mixing process. Add adsorbent or absorbent.
2.	Too much of hydrophobic lubricant e.g.: Magnesium-stearate.	Use a less amount of lubricant or change the type of lubricant.

Table No.8

The causes and remedies of lamination related to 'machine'

S.No.	Causes	Remedies
1.	Rapid relaxation of the peripheral regions of a tablet, on ejection from a die.	Use tapered dies, i.e. upper part of the die bore has an outward taper of 3° to 5°.
2.	Rapid decompression	Use pre-compression step. Reduce turret speed and reduce the final compression pressure.

Table No.9

1.8.2. Capping:

Definition:

'Capping' is the term used, when the upper or lower segment of the tablet separates horizontally, either partially or completely from the main body of a tablet and comes off as a cap, during ejection from the tablet press, or during subsequent handling.

Reason:

Capping is usually due to the air–entrapment in a compact during compression and subsequent expansion of tablet on ejection of a tablet from a die.

The causes and remedies of capping related to 'formulation' (granulation)

S.No.	Causes	Remedies
1.	Large amount of fines in the granulation	Remove some or all fines through 100 to 200 mesh screen
2.	Too dry or very low moisture content	Moisten the granules suitably. Add hygroscopic substance e.g.: sorbitol, methyl- cellulose or PEG-4000.
3.	Not thoroughly dried granules.	Dry the granules properly.
4.	Insufficient amount of binder or improper binder.	Increasing the mount of binder or Adding dry binder such as pre-gelatinized starch, gum acacia, powdered sorbitol, PVP, hydrophilic silica or powdered sugar.
5.	Insufficient or improper lubricant.	Increase the amount of lubricant or change the type of lubricant.

Table No.10

The causes and remedies of capping related to 'machine' (dies, punches and tablet press)

S.No.	Causes	Remedies
1.	Poorly finished dies	Polish dies properly. Investigate other steels or other materials.
2.	Deep concave punches or beveled-edge faces of punches.	Use flat punches.
3.	Lower punch remains below the face of die during ejection.	Make proper setting of lower punch during ejection.
4.	Incorrect adjustment of sweep-off blade.	Adjust sweep-off blade correctly to facilitate proper ejection.
5.	High turret speed.	Reduce speed of turret (Increase dwell time).

Table No.11

1.8.3. Chipping:

Definition:

'Chipping' is defined as the breaking of tablet edges, while the tablet leaves the press or during subsequent handling and coating operations.

Reason:

Incorrect machine settings, specially mis-set ejection take-off.

The causes and remedies of chipping related to 'formulation'

S.No.	Causes	Remedies
1.	Sticking on punch faces	Dry the granules properly or increase lubrication.
2.	Too dry granules.	Moisten the granules to plasticize. Add hygroscopic substances.
3.	Too much binding causes chipping at bottom.	Optimize binding, or use dry binders.

Table No.12

The causes and remedies of chipping related to 'machine'

S.No.	Causes	Remedies
1.	Groove of die worn at compression point.	Polish to open end, reverse or replace the die.
2.	Edge of punch face turned inside/inward.	Polish the punch edges
3.	Barreled die (center of the die wider than ends)	Polish the die to make it cylindrical
4.	Concavity too deep to compress properly	Reduce concavity of punch faces. Use flat punches.

Table No.13

1.8.4. Cracking:

Definition:

Small, fine cracks observed on the upper and lower central surface of tablets, or very rarely on the sidewall are referred to as 'Cracks'.

Reason:

It is observed as a result of rapid expansion of tablets, especially when deep concave punches are used.

The causes and remedies of cracking related to 'formulation'

S.No.	Causes	Remedies
1.	Large size of granules.	Reduce granule size. Add fines.
2.	Too dry granules.	Moisten the granules properly and add proper amount of binder.
3.	Tablets expand.	Improve granulation. Add dry binders.
4.	Granulation too cold.	Compress at room temperature.

Table No.14

The causes and remedies of cracking related to 'machine'

S.No.	Causes	Remedies
1.	Tablet expands on ejection due to air entrapment.	Use tapered die.
2.	Deep concavities cause cracking while removing tablets.	Use special take-off.

Table No.15

1.8.5. Sticking / Filming:

Definition:

'Sticking' refers to the tablet material adhering to the die wall.

'Filming' is a slow form of sticking and is largely due to excess moisture in the granulation.

Reason:

Improperly dried or improperly lubricated granules.

The causes and remedies of sticking related to 'formulation'

S.No.	Causes	Remedies
1.	Granules not dried properly.	Dry the granules properly. Make moisture analysis to determine limits.
2.	Too little or improper lubrication.	Increase or change lubricant.
3.	Too much binder	Reduce the amount of binder or use a different type of binder.
4.	Hygroscopic granular material.	Modify granulation and compress under controlled humidity.
5.	Too soft or weak granules.	Optimize the amount of binder and granulation technique.

Table No.16

The causes and remedies of sticking related to 'machine'

S.No.	Causes	Remedies
1.	Concavity too deep for granulation.	Reduce concavity to optimum.
2.	Too little pressure.	Increase pressure.
3.	Compressing too fast.	Reduce speed.

Table No.17

1.8.6. Picking:

Definition:

'Picking' is the term used when a small amount of material from a tablet is sticking to and being removed off from the tablet-surface by a punch face.

Reason:

Picking is of particular concern when punch tips have engraving or embossing letters, as well as the granular material is improperly dried.

The causes and remedies of picking related to 'formulation'

S.No.	Causes	Remedies
1.	Excessive moisture in granules.	Dry properly the granules, determine optimum limit.
2.	Too little or improper lubrication.	Increase lubrication; use colloidal silica as a 'polishing agent', so that material does not cling to punch faces.
3.	Low melting point substances, may soften from the heat of compression and lead to picking.	Add high melting-point materials. Use high meting point lubricants.
4.	Low melting point medicament in high concentration.	Refrigerate granules and the entire tablet press.
5.	Too warm granules when compressing.	Compress at room temperature. Cool sufficiently before compression.
6.	Too much amount of binder.	Reduce the amount of binder, change the type or use dry binders.

Table No.18

The causes and remedies of picking related to 'machine'

S.No.	Causes	Remedies
1.	Rough or scratched punch faces.	Polish faces to high luster.
2.	Embossing or engraving letters on punch faces such as B, A, O, R, P, Q, G.	Design lettering as large as possible. Plate the punch faces with chromium to produce a smooth and non-adherent face.
3.	Bevels or dividing lines too deep.	Reduce depths and sharpness.
4.	Pressure applied is not enough; too soft tablets.	Increase pressure to optimum.

Table No.19

1.8.7. Binding:

Definition:

'Binding' in the die, is the term used when the tablets adhere, seize or tear in the die. A film is formed in the die and ejection of tablet is hindered. With excessive binding, the tablet sides are cracked and it may crumble apart.

Reason:

Binding is usually due to excessive amount of moisture in granules, lack of lubrication and/or use of worn dies.

The causes and remedies of binding related to 'formulation'

S.No.	Causes	Remedies
1.	Too moist granules and extrudes around lower punch.	Dry the granules properly.
2.	Insufficient or improper lubricant.	Increase the amount of lubricant or use a more effective lubricant.
3.	Too coarse granules.	Reduce granular size, add more fines, and increase the quantity of lubricant.
4.	Too hard granules for the lubricant to be effective.	Modify granulation. Reduce granular size.
5.	Granular material very abrasive and cutting into dies.	If coarse granules, reduce its size. Use wear-resistant dies.
6.	Granular material too warm, sticks to the die.	Reduce temperature. Increase clearance if it is extruding.

Table No.20

The causes and remedies of binding related to machine

S.No	Causes	Remedies
1.	Poorly finished dies.	Polish the dies properly.
2.	Rough dies due to abrasion, corrosion.	Investigate other steels or other materials or modify granulation.
3.	Undersized dies. Too little clearance.	Rework to proper size. Increase clearance.
4.	Too much pressure in the tablet press.	Reduce pressure or Modify granulation.

Table No.21

1.8.8. Mottling:

Definition:

'Mottling' is the term used to describe an unequal distribution of colour on a tablet, with light or dark spots standing out in an otherwise uniform surface.

Reason:

One cause of mottling may be a coloured drug, whose colour differs from the colour of excipients used for granulation of a tablet.

The causes and remedies of 'mottling'

S.No.	Causes	Remedies
1.	A coloured drug used along with colourless or white-coloured excipients.	Use appropriate colourants.
2.	A dye migrates to the surface of granulation while drying.	Change the solvent system, Change the binder, Reduce drying temperature.
3.	Improperly mixed dye, especially during 'Direct Compression'.	Mix properly and reduce size if it is of a larger size to prevent segregation.
4.	Improper mixing of a coloured binder solution.	Incorporate dry colour additive during powder blending step, then add fine powdered adhesives such as acacia and tragacanth and mix well and finally add granulating liquid.

Table No.22

1.8.9. Double impression:

Definition:

'Double Impression' involves only those punches, which have a monogram or other engraving on them.

Reason:

At the moment of compression, the tablet receives the imprint of the punch. On some machines, the lower punch freely drops and travels uncontrolled for a short distance before riding up the ejection cam to push the tablet out of the die. During this free travel, the punch rotates and at this point, the punch may make a new impression on the bottom of the tablet, resulting in 'Double Impression'.

If the upper punch is uncontrolled, it can rotate during the short travel to the final compression stage and create a double impression.

The causes and remedies of double 'impression'

S.No.	Causes	Remedies
1.	Free rotation of either upper punch or lower punch during ejection of a tablet.	-Use keying in tooling, i.e. inset a key alongside of the punch, so that it fits the punch and prevents punch rotation. -Newer presses have anti-turning devices, which prevent punch rotation.

Table No.23

DISEASE INTRODUCTION

Malaria:

Quartan malaria; Falciparum malaria; Biduoterian fever; Blackwater fever; Tertian malaria; Plasmodium

Malaria is a tropical protozoan parasitic disease caused by *Plasmodium falciparum, P. vivax*, *P. ovale* and *P. malariae*. The disease is transmitted to human by the female *Anopheles* mosquito, during a blood meal. Of the four species *P. falciparum* is the most pathogenic responsible for about 40,000 million disability adjusted life years and an estimated 350–500 million malaria clinical episodes occur annually world wide.

Epidemiology:

Malaria causes about 400-900 million cases of fever and approximately 2-3 million deaths annually which represents one death every 15 seconds. The vast majority of cases occur in children under 5 years pregnant women are also especially vulnerable. Despite efforts to reduce transmission and increase treatment, there has been little change in areas who are at risk for the disease since 1992. In fact, if the prevalence of malaria continues on its course of continuous increase, the mortality rate could double in the next twenty years. The precise statistics are unknown because many cases occur in rural areas where people have no access to hospitals or resources to ensure health care. As a result, most cases remain undocumented.

Although co-infection of HIV with malaria mortality has increased, it remains a minor problem that the combination of HIV – TB.

Each year, 25-30 million people travel to tropical areas, and approximately 10,000-30,000 US and European travelers acquire malaria.

Around 60% of the cases and over 80% of the deaths due to malaria occur in Sub-Saharan Africa.

Geographic distribution of malaria and its incidence:

Malaria is endemic in most tropical and sub-tropical countries of sub-Saharan Africa, in large areas of the Middle East, South Asia, South East Asia, Oceania, Haiti, Central and South America and in parts of Mexico, North Africa and the Dominican Republic. It represents one of the largest scourges in third world countries, affecting approximately 300 - 500 million people, and killing three million people annually. In endemic areas, the number of malaria cases increases from time to time dramatically to an epidemic level. The population of Africa suffers the most from malaria, and it is reported that 90% of malaria cases are diagnosed in Africa, mainly among young children and pregnant women. It is reported that malaria causes the death of an African child every 30 seconds.

Geographic distribution of malaria (CENTERS FOR DISEASE CONTROL AND PREVENTION)

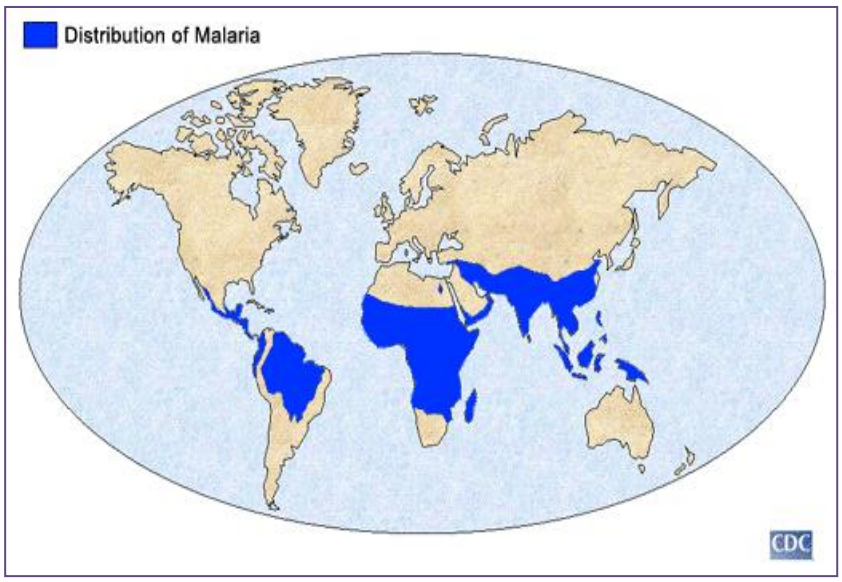


Fig.No.3

Risk factors

All human beings are at risk to acquire malaria. However, this tropical infection is more severe particularly in the following individuals:

- Children up to an age of 5 years
- Adults over 65 years old
- Pregnant women
- People treated with steroids or those receiving chemotherapy
- Patients with acquired HIV infection (Aids patients)
- Splenectomized people
- People suffering from porphyry, epilepsy or chronic illness

International occurrence

Malaria is responsible for approximately 1-3 million deaths per year, typically in children in sub-Saharan Africa infected with *P falciparum.* Populations at an increased risk for mortality due to malaria include primigravida individuals, travelers without immunity, and young children aged 6 months to 3 years who live in endemic areas.

Worldwide, an estimated 300-500 million cases occurring annually.[9] It is most prevalent in rural tropical areas below elevations of 1000 m [3282 ft] but is not limited to these climates. *P falciparum* is found mostly in the tropics and accounts for about 50% of cases and 95% of malarial deaths worldwide. *P vivax* is distributed more widely than *P falciparum,* but it causes less morbidity and mortality; however, both *P vivax* and *P ovale* can establish a hypnozoite phase in the liver, resulting in latent infection.

Human immunodeficiency virus [HIV] and malaria co-infection is a significant problem across Asia and sub-Saharan Africa, where both diseases are relatively common. Evidence suggests that malaria and HIV co-infection can lead to worse clinical outcomes in both disease processes, with malarial infections being more severe in patients infected with HIV and HIV replication increasing in malaria infection.

Young children aged 6 months to 3 years who live in endemic areas are at an increased risk of death due to malaria. Travelers without immunity are at an increased mortality risk, regardless of age.

Mortality

Internationally, malaria is responsible for approximately 1-3 million deaths per year. Of these deaths, the overwhelming majority are in children aged 5 years or younger, and 80-90% of the deaths each year are in rural sub-Saharan Africa. Malaria is the world's fourth leading cause of death in children younger than age 5 years.

Malaria is preventable and treatable. However, the lack of prevention and treatment due to poverty, war, and other economic and social instabilities in endemic areas results in millions of deaths each year.

MALARIAL LIFE CYCLE

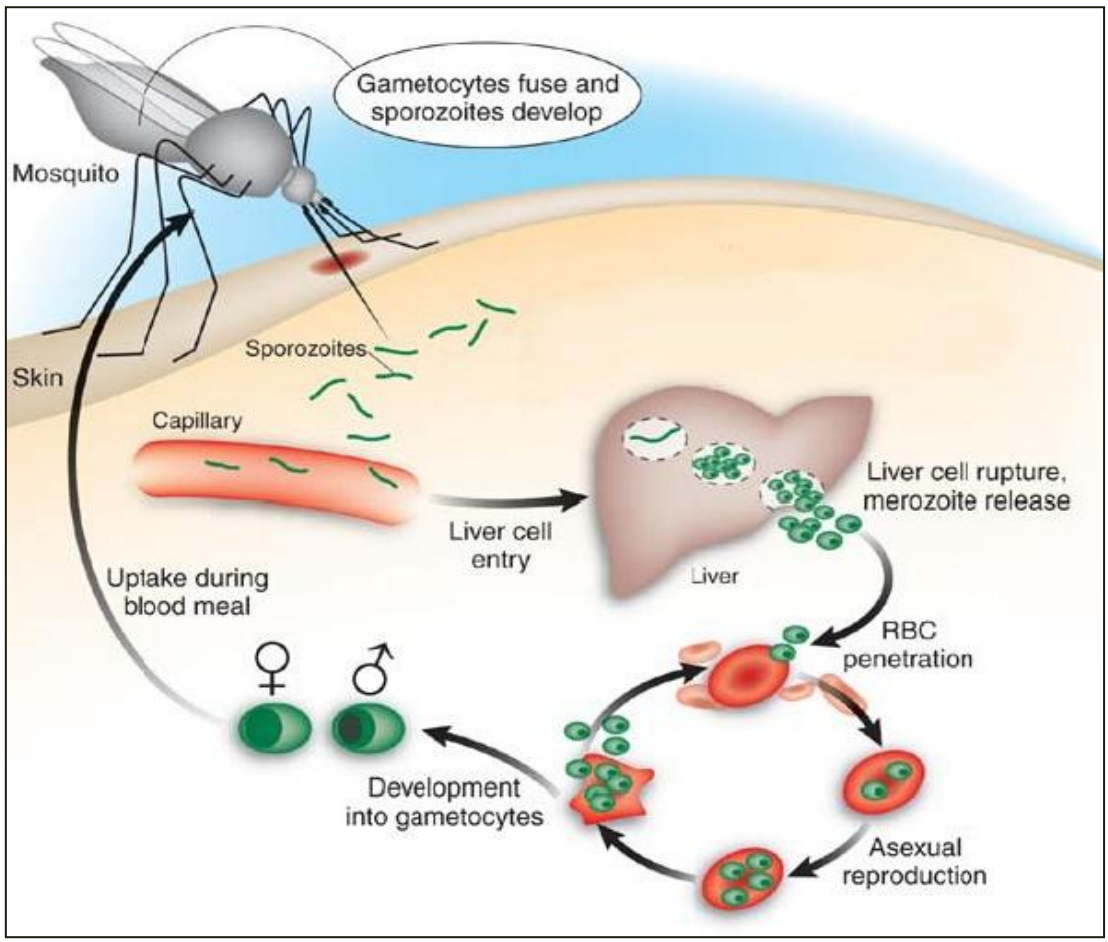


Fig. No.4

Causes, incidence, and risk factors:

Malaria is caused by a parasite that is passed from one human to another by the bite of infected Anopheles mosquitoes. After infection, the parasites [called sporozoites] travel through the bloodstream to the liver, where they mature and release another form, the merozoites. The parasites enter the bloodstream and infect red blood cells.

The parasites multiply inside the red blood cells, which then break open within 48 to 72 hours, infecting more red blood cells. The first symptoms usually occur 10 days to 4 weeks after infection, though they can appear as early as 8 days or as long as a year after infection. The symptoms occur in cycles of 48 to 72 hours.

Most symptoms are caused by:[3]

- The release of merozoites into the bloodstream
- Anemia resulting from the destruction of the red blood cells
- Large amounts of free hemoglobin being released into circulation after red blood cells break open
- Malaria can also be transmitted from a mother to her unborn baby [congenitally] and by blood transfusions. Malaria can be carried by mosquitoes in temperate climates, but the parasite disappears over the winter.
- The disease is a major health problem in much of the tropics and subtropics. The CDC estimates that there are 300-500 million cases of malaria each year and more than 1 million people die from it. It presents a major disease hazard for travelers to warm climates.
- In some areas of the world, mosquitoes that carry malaria have developed resistance to insecticides. In addition, the parasites have developed resistance to some antibiotics. These conditions have led to difficulty in controlling both the rate of infection and spread of this disease.
- There are four types of common malaria parasites. Recently, a fifth type, Plasmodium knowlesi, has been causing malaria in Malaysia and areas of southeast Asia. Another type, falciparum malaria, affects more red blood cells than the other types and is much more serious. It can be fatal within a few hours of the first symptoms.

Symptoms:

- Anaemia
- Bloody stools
- Chills
- Coma
- Convulsion
- Fever
- Headache
- Jaundice

- Muscle pain
- Nausea
- Sweating
- Vomiting

Signs and tests:

During a physical examination, the doctor may find an enlarged liver or enlarged spleen. Malaria blood smears taken at 6 to 12 hour intervals confirm the diagnosis.

A complete blood count [CBC] will identify anemia if it is present.

Treatment:

Malaria, especially Falciparum malaria, is a medical emergency that requires a hospital stay. Chloroquine is often used as an anti-malarial medication. However, chloroquine-resistant infections are common in some parts of the world.

Possible treatments for chloroquine-resistant infections include:

- The combination of quinidine or quinine plus doxycycline, tetracycline, or clindamycin
- Atovaquone plus proguanil [Malarone]
- Mefloquine or artesunate
- The combination of pyrimethamine and sulfadoxine [Fansidar]
- The choice of medication depends in part on where you were when you were infected.
- Medical care, including fluids through a vein [IV] and other medications and breathing [respiratory] support may be needed.

Expectations: [prognosis]

The outcome is expected to be good in most cases of malaria with treatment, but poor in P falciparum infection with complications.

Complications:

Most complications are caused by *P falciparum*. One of them is cerebral malaria, defined as coma, altered mental status, or multiple seizures with *P falciparum* in the blood. Cerebral malaria is the most common cause of death in patients with malaria. If untreated, this complication is lethal. Even with treatment, 15% of children and 20% of adults who develop cerebral malaria die. The symptoms of cerebral malaria are similar to those of toxic encephalopathy. Other complications of *P falciparum* infection include the following:

- Seizures - Secondary to either hypoglycemia or cerebral malaria
- Renal failure - As many as 30% of nonimmune adults infected with *P falciparum* suffer acute renal failure
- Hypoglycemia
- Hemoglobinuria [blackwater fever] - Blackwater fever is the passage of dark urine, described as Madeira wine colored; hemolysis, hemoglobinemia, and the subsequent hemoglobinuria and hemozoinuria cause this condition
- Noncardiogenic pulmonary edema - This affliction is most common in pregnant women and results in death in 80% of patients
- Profound hypoglycemia - Hypoglycemia often occurs in young children and pregnant women; it often is difficult to diagnose because adrenergic signs are not always present and because stupor already may have occurred in the patient
- Lactic acidosis - This occurs when the microvasculature becomes clogged with *P falciparum*; if the venous lactate level reaches 45 mg/dL, a poor prognosis is very likely
- Hemolysis resulting in severe anemia and jaundice
- Bleeding [coagulopathy]
- Brain infection [cerebritis]
- Liver failure
- Rupture of the spleen leading to massive internal bleeding [hemorrhage].

Prevention:

Most people who live in areas where malaria is common have gotten some immunity to the disease. Visitors will not have immunity, and should take preventive medications.

It is important to see your health care provider well before your trip, because treatment may need to begin as long as 2 weeks before travel to the area, and continue for a month after you leave the area. In 2006, the CDC reported that most travelers from the U.S. who contracted malaria failed to take the right precautions.

The types of anti-malarial medications prescribed will depend on the area you visit. According to the CDC, travelers to South America, Africa, the Indian subcontinent, Asia, and the South Pacific should take one of the following drugs: mefloquine, doxycycline, chloroquine, hydroxychloroquine, or Malarone. Even pregnant women should take preventive medications because the risk to the fetus from the medication is less than the risk of catching this infection.

People who are taking anti-malarial medications may still become infected. Avoid mosquito bites by wearing protective clothing over the arms and legs, using screens on windows, and using insect repellent.

Chloroquine has been the drug of choice for protecting against malaria. But because of resistance, it is now only suggested for use in areas where Plasmodium vivax, P. oval, and P. malariae are present. Falciparum malaria is becoming increasingly resistant to anti-malarial medications.

For travelers going to areas where Falciparum malaria is known to occur, there are several options for malaria prevention, including mefloquine, atovaquone/proguanil [Malarone], and doxycycline.

ANTIMALARIAL DRUGS

Antimalarial drugs

These are drugs used for prophylaxis, treatment and prevention of relapses of malaria. It is endemic in most parts of India and other tropical countries. It is one of the major health problems.

As per latest WHO estimates there are 300-500 million new clinical cases globally and >1 million deaths occur due to malaria each year, 90% of which are in Africa.

In India the National Malaria Eradication Programme [NMEP], started in 1958, achieved near complete disappearance of the disease in 1960s. However, due to the development of insecticide resistance among mosquitoes and other factors, it staged a comeback in the mid 1970s [6.47 million cases in 1976], and continues to prevail in endemic/ subendemic proportions in different areas.

Conceding that eradication of malaria is not possible, NMEP was renamed National Antimalaria Programme [NAMP].

Its scope has now been widened to include other vector borne diseases, and it is called "National Vector borne diseases control programme" [NVBDCP].

For the year 2005, the NVBDCP has reported 1.8 million slides proven malaria cases in India, out of which ≈44% were falciparum malaria with 963 deaths.

The WHO estimates that actual number of malaria cases in India is 6 times more, i.e. ~12 million.

History of Antimalarial drugs:

- The bark of cinchona introduced in early 17^{th} century as a cure for fevers.
- Later Quinine, isolated from cinchona bark in 1820 and used till 1942.
- Mepacrine was produced in germany in 1926 and extensively field tested by the Allies during world war 2.

- Chloroquine was produced in USA soon after as a less toxic alternative to mepacrine.
- Proguanil was introduced in1945 by the British as a well tolerated clinical alternative.
- None of the above drugs were found to be capable of preventing relapses in vivax malaria.
- Pamaquine tested in 1920s and primaquine emerged as the most desirable drug. No attention paid to these drugs because of poor schizontocide action.
- Pyrimethamine was produced in 1951 under a planned post-war research programme for antimalarial drugs.
- The most important additions of the recent years are Mefloquine, ARTEMISININ and its derivatives/ congeners, pyronaridine and few other synthetic compounds for resistant falciparum malaria.

Classification of antimalarial drugs:

- 4 – Aminoquinolines - Chloroquine, Amodiaquine, Piperaquine.
- Quinoline – methanol - Mefloquine.
- Cinchona alkaloid - Quinine, Quinidine.
- Biguanides - Proguanil, Chlorproguanil.
- Diaminopyrimidines - Pyrimethamine.
- 8 – aminoquinoline - Primaquine, Bulaquine.
- Sulfonamides and Sulfone - Sulfadoxine, Sulfamethopyrazine, Dapsone.
- Tetracyclines - Tetracycline, Doxycycline.
- Sesquiterpine lactones - Artesunate, Artemether, Arteether.
- Amino alcohols - Halofantrine, Lumefantrine.
- Mannich base - Pyronaridine.
- Naphthoquinone - Atovaquone.

The use of a single first-line therapy effective against both P. vivax and P. falciparum would be ideal in view of the frequent co-endemicity of the two species and the increasing resistance of parasites to chloroquine.

The widespread adoption of artemisinin-based combination therapies [ACTs] as highly effective first-line therapy for P.falciparum has prompted a closer examination of their role in the management of P.vivax malaria.

This project work considers the available evidence relating to the potential role of artemether-lumefantrine [AL], the most widely used ACT worldwide, in the management of vivax malaria. P. vivax Life Cycle and Implications for the Evaluation of Efficacy of Antimalarials

In contrast to P. falciparum, P. vivax forms hypnozoites that can remain dormant in the parenchymal cells of the host liver following an acute infection. After an interval of time, which varies in duration depending on the geographical area , the hypnozoites can mature into hepatic schizonts that rupture to release merozoites capable of infecting erythrocytes and inducing a spontaneous relapse [Figure 1]. Clinically, relapses present as a new malaria episode, indistinguishable from a new infection.

P. vivax life cycle and sites of action for different Antimalarials.

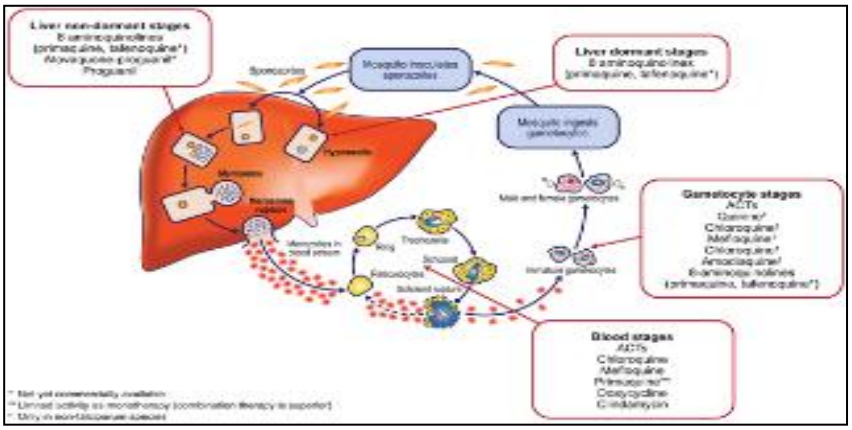


Fig.No.5

Thus, in P. vivax infections, the eradication of blood schizonts is not sufficient to control the disease, and an effective treatment requires killing the hypnozoites [“radical cure”] to prevent future relapses.

Chloroquine, an inexpensive and effective treatment for vivax malaria in most areas of the world has been the mainstay first-line therapy for this species for the past seven decades.

It is still WHO's recommended drug for vivax, but needs to be combined with primaquine, currently the only approved drug capable of achieving radical cure of hypnozoites. WHO guidelines state that primaquine needs to be administered daily for 14 d to achieve this purpose, although the efficacy of shorter courses is being investigated.

Chloroquine achieves parasitological cure at day 28 in more than 90% of chloroquine-sensitive P. vivax infections, but in many areas of the world, significant levels of resistance to this drug in P. vivax have been documented, notably in Indonesia [<50% probability of therapeutic success] and to a lesser extent in India, Myanmar, Turkey, the Brazilian Amazon, and Colombia.

Worryingly, there is also growing evidence of clinical resistance of vivax to Chloroquine in Africa.

Emergence of resistance to Chloroquine, particularly in view of the potentially serious consequences of vivax infection, adds a further urgency to providing effective therapy.

The possibility of relapse brings about uncertainty when assessing the efficacy of Antimalarial drugs that have an effect on asexual stages of the life cycle but not on the dormant liver forms.

Thus, patients correctly treated with an Antimalarial with no Antihypnozoite activity may present with recurrent post-treatment parasitemia that can derive from one of three sources:

[1] Reappearing parasites as a result of the incomplete clearance of the original infection [recrudescence], often the consequence of ineffective or incomplete treatment,

[2] Generation of de novo parasitemia from the liver reservoirs [relapse], or

[3] Parasites ensuing from a new and independent infection [new infection].

Parasites in recrudescent or relapsing infections may be genetically identical to the original infection and thus impossible to differentiate with current technology.

Some reports state that over half of the relapsing parasites may be genetically different from the preceding documented infection, but this may be explained by older heterologous hypnozoites becoming reactivated.

A new infection arising from the bite of an infected vector, however, may differ from the original infecting parasite such that they can be distinguished from one another by PCR molecular techniques.

A pragmatic solution to this investigative hurdle has been adopted whereby any new parasitemia appearing before day 16 is by convention directly classified as recrudescence [i.e., treatment failure] because of the unlikelihood of the infection being a relapse within such a short space of time, and because this is the minimum incubation period for a new infection to appear in peripheral blood. Reappearance of parasites after day 16 cannot be assumed to be recrudescence.

Possible sources of residual blood parasitemia after initial treatment and possible genetic similarity or dissimiliarity.

ACTs in Vivax Malaria

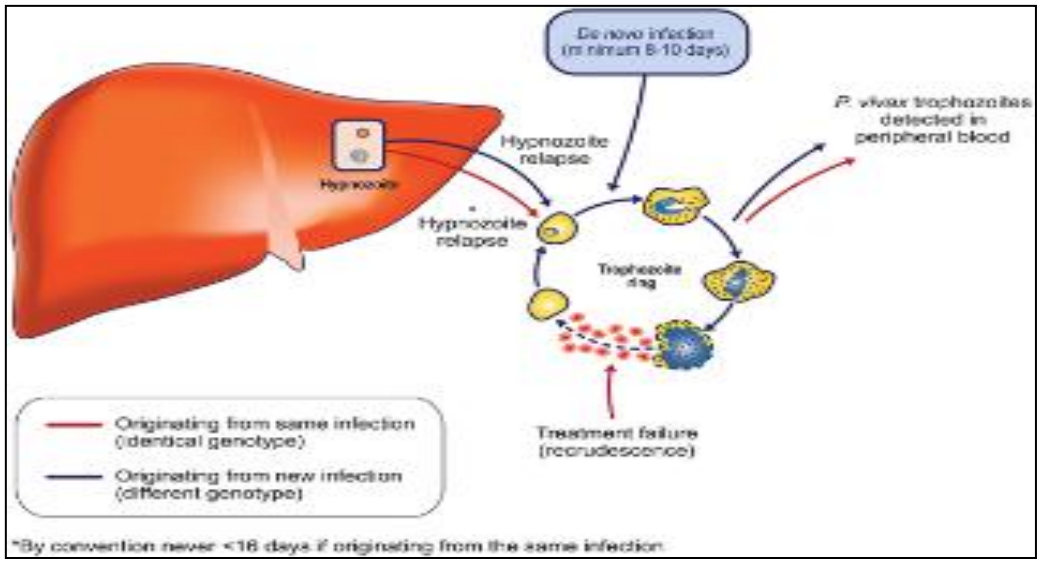


Fig. No.6

ACTs are highly effective against uncomplicated P. falciparum malaria and are now recommended as first-line therapy, having been adopted in most countries where P. falciparum is endemic.

Most ACTs show high and similar efficacy against the blood stages of P. vivax, but none is active against the hepatic P. vivax hypnozoites responsible for relapse.

Therefore, in order to achieve radical cure, similar to Chloroquine treatment, ACT treatment must be complemented with a full course of primaquine.

Where both P. vivax and P. falciparum species are prevalent and ACTs have been adopted as first-line therapy for P. falciparum, use of a unified first-line therapy based on ACTs would simplify treatment procurement, distribution, and management, offering interesting logistical benefits.

ACT therapy for both types of infections would also avoid the problem of P. falciparum being mistakenly diagnosed as P. vivax and inadequately treated with Chloroquine in the many regions where diagnosis is based on clinical symptoms alone.

In areas of Chloroquine-resistant P. vivax, and where ACTs have already been adopted for the treatment of P. falciparum malaria, ACTs could also be used for the treatment of vivax, provided they are complemented with the standard Primaquine course.

Indeed, at least four countries have now adopted a unified first-line therapy based on ACTs: the Solomon Islands, Vanuatu, and Papua New Guinea deploy AL, while Indonesia deploys Dihydroartemisinin-piperaquine [DHA-PQP] in Papua.

COMBINATION THERAPY[2,5]

Combination therapy or polytherapy is the use of more than one medication or other therapy. In contrast, monotherapy is any therapy which is taken by itself.

Definition:

Combination drug therapy is defined as the use of 2 or more pharmacologic agents administered separately or in a fixed-dose combination of 2 or more active ingredients in a single-dosage formulation. Combination therapy is frequently prescribed by physicians to treat and manage a plethora of medical conditions;

Most often, these terms refer to the simultaneous administration of two or more medications to treat a single disease. However, the expression is also used when other types of therapy are used at the same time, such as the combination of medications and talk therapy to treat depression.

Combination therapy may be achieved by giving separate drugs, or, where available, by giving combination drugs, which are dosage forms that contain more than one active ingredient.

Polypharmacy is the use of multiple medications to treat multiple, separate diseases.

Uses for combination therapy:

Conditions treated with combination therapy include tuberculosis, leprosy, cancer, malaria, and HIV/AIDS. One major benefit of combination therapies is that they reduce development of drug resistance, since a pathogen or tumor is less likely to have resistance to multiple drugs simultaneously. Artemisinin-based monotherapies for malaria are explicitly discouraged to avoid the problem of developing resistance to the newer treatment.

Combination therapy may seem costlier than monotherapy in the short term, but when used appropriately, it causes significant savings: lower treatment failure rate, lower case-fatality ratios, slower development of resistance and consequently, less money needed for the development of new drugs.

Uses for monotherapy:

Monotherapy can be applied to any therapeutic approach, but it is most commonly used to describe the use of a single medication. Normally, monotherapy is selected because a single medication is adequate to treat the medical condition. However, monotherapies may also be used because of unwanted side effects or dangerous drug interactions.

Combination therapy:

Following increased resistance of malaria parasites to conventional drugs in the malarial regions of the world, the WHO is promoting artemisinin-based combination therapy (ACT) for treating uncomplicated malaria. The objective of this report is to review the available scientific information on the efficacy, safety, resistance and policy implementation of ACT as it relates to sub-Saharan Africa since the Abuja 2000 Roll Back Malaria initiative. To achieve this, a Medline search was performed to identify scientific publications relevant to the review. The data reviewed indicated that ACT proved very effective in the treatment of uncomplicated Plasmodium falciparum malaria in the region. ACT was shown to be effective, safe and tolerable

and no resistance has been detected so far. However, the major challenges to its widespread use in the region include its high cost, low drug quality and poor healthcare delivery systems, among others. It is absolutely imperative for sub-Saharan African countries to establish an effective national antimalarial drug policy which will provide safe, effective, high-quality, accessible and affordable antimalarial drugs such as ACT to the populations at risk of malaria but, at the same time, promote rational drug use in order to delay or prevent the development of antimalarial drug resistance.

Cellular pathways operate more like webs than superhighways. There are multiple redundancies, or alternate routes, that may be activated in response to the inhibition of a pathway. This redundancy promotes the emergence of resistant cells or organisms under the selective pressure of a targeted agent, resulting in drug resistance and clinical relapse. For this reason, combination therapies are often needed to effectively treat many tumors and infectious diseases.

Concern has been expressed that the policies of the Food and Drug Administration (FDA) on the development of combination therapies, which heretofore have focused primarily on fixed-dose combinations (i.e., combined in the same tablet or vial) of already-marketed drugs, are a barrier to the development of novel combination regimens using targeted therapies.1 FDA regulations for fixed-dose combinations require demonstration of the contribution of each component of the combination to the treatment effect. Often, a large clinical trial, using a multigroup factorial design to demonstrate that the combination is superior to each of the individual components alone, is needed to meet this requirement. For example, a factorial study for a two-drug combination could have four groups so that the combination can be compared with each of the individual components alone, as well as with either the standard of care or placebo.

The development of effective therapies for serious diseases is a primary FDA objective. The agency recognizes the therapeutic potential of innovative combination therapies and is committed to fostering their development. The FDA

also recognizes the uncertainties inherent in combination development programs and is equally committed to effectively managing those risks.

Conclusion:

Combination drug therapy is often necessary for the management and treatment of various chronic medical conditions, including CVD, hypertension, diabetes and malaria.

As more fixed-dose combination formulations become available, they should be considered for use with the aims of improving patient adherence, simplifying drug regimens, and optimizing care.

Patients should be encouraged to maintain routine visits with their primary health care provider so they can be properly monitored.

Although studies have shown that combination drug therapy is often beneficial for the treatment of many patients, pharmacists are vital to ensuring that these agents are used appropriately by screening for potential drug–drug interactions, contraindications such as hepatic or renal problems, and unnecessary drug use.

2. LITERATURE REVIEW

1**] David Joseph Diemert et al,**[36] The George Washington University Medical Center, United States of America December 27, 2011 has done research in the Use of Artemether-Lumefantrine for the Treatment of Uncomplicated Plasmodium vivax Malaria. A unified treatment strategy for both falciparum and vivax infections using ACTs that have already been deployed in many malaria-endemic areas of the world would offer important logistical and cost advantages, especially in areas of high chloroquine resistance or where parasitological diagnosis remains challenging. The efficacy of AL against the blood stages of P. vivax seems clear, showing rapid parasite and fever clearance.

2] **Michael Makanga, et al,**[37] 12 October 2009, researched in the clinical efficacy of artemether / lumefantrine [Coartem®], Current World Health Organization [WHO] guidelines for the treatment of uncomplicated falciparum malaria recommend the use of artemisinin-based combination therapy [ACT]. Artemether/lumefantrine is an ACT prequalified by the WHO for efficacy, safety and quality, approved by Swissmedic in December 2008 and recently approved by the USA FDA. Coartem® is a fixed-dose combination of artemether and lumefantrine. Its two components have different modes of action that provide synergistic anti-malarial activity. It is indicated for the treatment of infants, children and adults with acute, uncomplicated infection due to Plasmodium falciparum or mixed infections including P. falciparum. The efficacy of the six-dose regimen of artemether/lumefantrine has been confirmed in many different patient populations around the world, consistently achieving 28-day PCR [polymerase chain reaction]-corrected cure rates of >95% in the evaluable population, rapidly clearing parasitaemia and fever, and demonstrating a significant gametocidal effect, even in areas of widespread parasite resistance to other antimalarials.

3] **J.Sunil, et.al,**[38]vol.2,4 2010, IJPPS, has developed HPLC method development and validation for simultaneous estimation of Artemether and Lumefantrine in

pharmaceutical dosage forms. A simple and precise HPLC method was developed for the estimation of artemether and lumifantrine in pure and pharmaceutical dosage forms. The quantification was carried out using symmetry C 18, 250 × 4.6 mm , i.d , 5µm partical size in isocratic mode , with mobile phase compressing of buffer and acetonitrile in the ratio of 40:60 [v/v] PH 3 ±0.5. Flow rate was 1.5 m/min and detection carried out by uv detector dual 210 and 303 nm. The retention times were 13.887 and 7.218 mins for artemether and lumefantrine, respectively. The percentage recovery was found to be 98.87 and 99.78% for artemether and lumefantrine, respectively.

4] **Naawa Sipilanyambe et al,**[39] 29 January 2008, A decision was made to change national drug policy to artemether-lumefantrine [AL] in the first quarter of 2002, with a formal announcement made in October 2002. During this period, efforts were undertaken to identify funding for the procurement of AL and to develop new malaria treatment guidelines, training materials, and plans for implementation of the policy. In order to avoid a delay in implementation, the policy change decision required a formal adoption within existing legislation. Starting with donated drug, a phased deployment of AL began in January 2003 with initial use in seven districts followed by scaling up to 28 districts in the second half of 2003 and then to all 72 districts countrywide in early 2004.

5] **Abdulla et al**,[40] licensee BioMed Central Ltd. 3 September 2010, developed a Early clinical development of artemether-lumefantrine dispersible tablet: palatability of three flavours and bioavailability in healthy subjects. Efforts to ease administration and enhance acceptability of the oral anti-malarial artemether-lumefantrine [A-L] crushed tablet to infants and children triggered the development of a novel dispersible tablet of A-L. During early development of this new formulation, two studies were performed in healthy subjects, one to evaluate the palatability of three flavours of A-L, and a second one to compare the bioavailability of active principles between the dispersible tablet and the tablet [administered crushed and intact].

6] **P Umapathi et al**,[41] oct 2011,tjpr has reasearched in development and validation of a dissolution test method for Artemether and Lumefantrine in tablets. A single dilution method for evaluating the invitro release of artemether and Lumefantrine from tablets was developed and evaluated. The dissolution medium of 1000 ml of 2% w/v of Myrj 52 in 0.0052M Hcl per vessel with the paddle rotation of 100 to 120 per minute. The dissolution samples were analysed using a Water HPLC system C-18. The mobile phase was a mixture of 20 volumes of 0.5 %v/v/of triethylamine in water [PH 3.0 with orthophosphoric acid] and 80 volumes of acetonitrile. The detection wavelength was set at 216 nm and 100 µl of each sample was injected. The dissolution test provided sink conditions for Artemether and Lumefantrine and was able to discriminate between tablet formulations of different hardness and direct composition.

7] **Pauline Byakika et al**,[42] 14 February 2011, has researched in Artemether-Lumefantrine Combination Therapy for Treatment of Uncomplicated Malaria: The Potential for Complex Interactions with Antiretroviral Drugs in HIV-Infected Individuals. Treatment of malaria in HIV-infected individuals receiving antiretroviral therapy [ART] poses significant challenges. Artemether-lumefantrine [AL] is one of the artemisisnin-based combination therapies recommended for treatment of malaria. The drug combination is highly efficacious against sensitive and multidrug resistant falciparum malaria. Both artemether and lumefantrine are metabolized by hepatic cytochrome P450 [CYP450] enzymes which metabolize the protease inhibitors [PIs] and nonnucleoside reverse transcriptase inhibitors [NNRTIs] used for HIV treatment. Coadministration of NNRTIs and PIs with AL could potentially cause complex pharmacokinetic drug interactions. NNRTI by inducing CYP450 3A4 enzyme and PIs by inhibiting CYP450 3A4 enzymes could influence both artemether and lumefantrine concentrations and their active metabolites dihydroartemisinin and desbutyl-lumefantrine, predisposing patients to poor treatment response, toxicity, and risk for development of resistance. There are scanty data on these interactions and their consequences. Pharmacokinetic studies to evaluate these interactions in the target populations are urgently needed.

8] Aika AA Omari et al, 2009[43] The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd. Artemether-lumefantrine [six-dose regimen] for treating uncomplicated falciparum malaria.Malaria is a parasitic disease, spread by mosquitoes. It affects millions of people worldwide, and causes significant illness and mortality. Uncomplicated malaria presents with symptoms such as fever, headache, muscle pain, and vomiting. The parasite has become resistant to a number of previously effective drugs, and so combinations of drugs are used to try increase cure and to prevent further resistance.Artemether-lumefantrine is one such drug combination. This review of trials showed that the six-dose regimen of artemether-lumefantrine was associated with high cure rates and was more effective that most other drug combinations used for uncomplicated malaria. Further research is needed to properly assess adverse outcomes. The fixed-dose combination of artemether-lumefantrine, called co-artemether, contains 20mg of artemether and 120mg of lumefantrine [previously called benflumetol]. It was initially developed by scientists at the Academy ofMilitaryMedical Sciences in China before the pharmaceutical company Novartis [Switzerland] became a partner and was licensed to market it as Coartem® or Riamet. This oral preparation has been designed for use against chloroquine-resistant falciparum malaria.

9] **Naawa Sipilanyambe–et al,**[44] *Malaria Journal* 2008 biomed, Convincing evidence of the failing efficacy of chloroquine resulted in the initiation of a process that eventually led to the development and implementation of a new national drug policy based on artemisinin-based combination therapy [ACT]. the transition to effective malaria case-management strategies including efficacious ACT is a fundamental cornerstone for malaria control. These policy changes are not without difficulties and demand a sustained international financing strategy for them to succeed. The Zambian experience demonstrates the need for a harmonized national consensus among many stakeholders and a political commitment to ensure that new policies are translated into practice quickly. To guarantee effective policies become ssa health system and not a drug issue.

10] Billy E Ngasala et al,[45] Effectiveness of artemether-lumefantrine provided by community health workers in under-five children with uncomplicated malaria in rural Tanzania: an open label prospective study.An open label, single arm prospective study was conducted in two rural villages with high malaria transmission in Kibaha District, Tanzania. Children presenting to CHWs with uncomplicated fever and a positive rapid malaria diagnostic test [RDT] were provisionally enrolled and provided AL for unsupervised treatment at home. Patients with microscopy confirmed *P. falciparum* parasitaemia were definitely enrolled and reviewed weekly by the CHWs during 42 days. Primary outcome measure was PCR corrected parasitological cure rate by day 42, as estimated by Kaplan-Meier survival analysis. This trial is registered with ClinicalTrials.gov, number NCT00454961. Provision of AL by CHWs for unsupervised malaria treatment at home was highly effective, which provides evidence base for scaling-up implementation of HMM with AL in Tanzania.

11] Rod Ibara-Okabande et al,[46] Malaria Journal 2012 Reduction of multiplicity of infections but no change in msp2 genetic diversity in Plasmodium falciparum isolates from Congolese children after introduction of artemisinin-combination therapy. This study shows that the introduction of ACT in the Republic of Congo has reduced the multiplicity of infection but not the genetic diversity of P. falciparum isolates from children living in Southern districts of Brazzaville. It also points out that children exposed to the same malaria transmission and socio-economic conditions might have different susceptibility to malaria infections. The two groups described here are important for designing additional studies to investigate human and parasite genetic factors that may be involved in the susceptibility/resistance to malaria in this area.

12] **Abdallah et al,**[47] Malaria Journal 2012, The spread of multidrug-resistant Plasmodium falciparum malaria in Sudan [10,11] has led to adoption of artemisinin-based combination therapy [ACT], with artesunate–sulphadoxine–pyrimethamine [AS–SP] and artemether–lumefantrine [AL] becoming the recommended first- and secondline treatments for uncomplicated P. falciparum malaria, respectively. ACT is highly effective against uncomplicated P. falciparum malaria and, as a consequence

of high levels of chloroquine resistance, is now widely adopted as the first-line therapy in most malaria endemic countries, including Sudan [10]. Indeed, some countries such as Papua New Guinea and Indonesia have adopted ACT as the first-line therapy for P. vivax and P. falciparum malaria [16]. A policy whereby use of a unified first-line therapy based on ACT was implemented could have great public health value in that it would simplify treatment, management and logistics of malaria disease control. It should be mentioned that chloroquine is no longer registered or available for use in Sudan, so as to avoid the problem of P. falciparum infection being treated with chloroquine.

13**] Vaughan-Williams et al.**[48] Malaria Journal 2012, Assessment of the therapeutic efficacy of artemether-lumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in northern KwaZulu-Natal: an observational cohort study. artemether-lumefantrine has been used as first-line treatment for uncomplicated Plasmodium falciparum malaria in northern KwaZulu-Natal since 2001, its efficacy has not been assessed since 2002. The objectives of this study were to quantify the proportion of patients treated for uncomplicated P. falciparum malaria with artemether-lumefantrine who failed treatment after 28 days, and to determine the prevalence of molecular markers associated with artemether-lumefantrine and chloroquine resistance. An observational cohort of 49 symptomatic patients, diagnosed with uncomplicated P. falciparum malaria by rapid diagnostic test, had blood taken for malaria blood films and P. falciparum DNA polymerase chain reaction [PCR]. Following diagnosis, patients were treated with artemether-lumefantrine [CoartemW] and invited to return to the health facility after 28 days for repeat blood film and PCR. All PCR P. falciparum positive samples were analysed for molecular markers of lumefantrine and chloroquine resistance.

14] **Faye et al. Malaria Journal 2012**,[49] Multicentre study evaluating the non-inferiority of the new paediatric formulation of artesunate/ amodiaquine versus artemether/lumefantrine for the management of uncomplicated Plasmodium falciparum malaria in children in Cameroon, Ivory Coast and Senegal. to evaluate the non-inferiority of the new paediatric formulation of artesunate/amodiaquine

[AS+AQ][Camoquin-Plus PaediatricW] in suspension form versus artemether/lumefantrine [AL][CoartemW] in the management of African children with uncomplicated falciparum malaria. It was an open randomized trial including children aged between 7 months and 7 years. The endpoints were Adequate Clinical and Parasitological Response [ACPR] at day 28, the clinical and biological tolerability. Statistical analyses were done in Intention to Treat [ITT] and in Per protocol [PP]. At the end of the study 481 patients were enrolled in the three countries [249 in the AS+AQ arm and 232 in the AL arm]. ACRP in ITT after PCR correction did not show any statistical difference between the two groups with 97.6% for AS+AQ versus 94.8% for AL. In the PP analysis, the corrected ACRP were respectively 98.7% and 96.9% for the two regimens. The clinical tolerance was good without significant difference. Anaemia was significantly higher at D7 in the two groups compared to D0.This study demonstrates the non-inferiority of AS+AQ versus AL, its efficacy and tolerance in the management of uncomplicated Plasmodium falciparum malaria in African children.

15] **Tajeldin M Abdallah et al,**[50] Malaria Journal 2012, Efficacy of artemether-lumefantrine as atreatment for uncomplicated Plasmodium vivaxmalaria in eastern Sudan. Artemisinin-based combination therapy [ACT] is the treatment of choice for uncomplicated Plasmodium falciparum malaria in most areas of the world, where malaria is endemic, including Sudan. However, few published data are available on the use of ACT for treatment of P. vivax malaria. This study was conducted at a health centre in Kassala, eastern Sudan, from October to December 2011. Patients with uncomplicated P. vivax malaria received artemether-lumefantrine [AL] tablets [containing 20mg artemether and 120 mg lumefantrine] and were monitored for 28 days. Out of the 43 cases enrolled in this study, 38 completed the 28-day follow-up. Their mean age was 25.1 years [SD: 1.5]. On day 3 following AL treatment, all of the patients were afebrile and aparasitaemic. By day 28, all 38 patients exhibited adequate clinical and parasitological responses to AL treatment. The cure rate was 100% and 88.4% for the per protocol analysis andfor the intention to treat analysis, respectively. Mild adverse effects [nausea, vomiting, abdominal pain, dizziness

and/or rash] that resolved spontaneously were observed in four [10.5%] of the patients. AL combination therapy was fully effective for treatment of P. vivax malaria in the study in eastern Sudan.

16] **Shretta and Yadav Malaria Journal 2012**,[51] Stabilizing supply of artemisinin and artemisinin-based combination therapy in an era of wide-spread scale-up. The global demand for artemisinin-based combination therapy [ACT] has grown sharply since its recommendation by the World Health Organization in 2002. However, a combination of financing and programmatic uncertainties, limited suppliers of finished products, information opacity across the different tiers in the supply chain, and widespread fluctuations in raw material prices have together contributed to a market fraught with demand and supply uncertainties and price volatility. Various short-term solutions have been deployed to alleviate supply shortages caused by these challenges; however, new mechanisms are required to build resilience into the supply chain. This review concludes that a mix of strategies is required to stabilize the artemisinin and ACT market. First, better and more effective pooling of demand and supply risks and better contracting to allow risk sharing among the stakeholders are needed. Physical and financial buffer stocks will enable better matching of demand and supply in the short and medium term. Secondly, physical buffers will allow stable supplies when there are procurement and supply management challenges while financial buffer funds will address issues around funding disruptions.

Finally, in the medium to long term, significant investments in country level system strengthening will be required to minimize national level demand uncertainties. In addition a voluntary standard for extractors to ensure appropriate purchasing and sales practices as well as minimum quality and ethical standards could help stabilize the artemisinin market in the long term.

17**] Abuaku et al.**[52] Malaria Journal 2012, Therapeutic efficacy of artemether-lumefantrine combination in the treatment of uncomplicated malaria among children under five years of age in three ecological zones in Ghana. AL remains efficacious in Ghana with significant ecologic zonal differences. The savannah zone may be a

potential zone for any emergence of resistant alleles as a result of the slower parasite clearance observed in the zone. Pharmacokinetic studies will be useful in future anti-malarial drug resistance surveillance activities in Ghana to better describe treatment failures. Ghana's policy of multiple first-line therapy is in the right direction, and needs to be supported by all stakeholders as it delays the emergence and slows spread of drug resistance [28,29]. Furthermore, the WHO criteria for ETF may need to be reviewed following the observation that all 5 children classified as ETF on the basis of parasite count on day-2 being greater than parasite count on day-0 cleared all parasites on day-3, without any rescue treatment, and remained aparasitaemic during the follow-up period.

18] **Kayentao et al,**[53] Malaria Journal 2012, Artemisinin-based combination therapy [ACT] is the mainstay of global efforts for treatment of Plasmodium falciparum malaria, but decline in its efficacy is the most important obstacle towards malaria control and elimination. Therefore, the present molecular analysis provides information on putative mutations associated with artemisinin resistance in P. falciparum clinical population unexposed and exposed to artesunate 4 years after adoption of ACT as the first-line anti-malarial therapy in Iran. Molecular assessment of atpase6 mutations associated with artemisinin resistance among unexposed and exposed Plasmodium falciparum clinical isolates to artemisinin-based combination therapy. Results: Neither the pfatpase6 L263E nor the A623E mutation was detected among all examined isolates. The E431K mutation was found in 23% of the analysed samples unexposed to ACT; however, it was detected in 17.8% [34/191] of P. falciparum isolates exposed to artesunate after 2007. High frequency of this single nucleotide polymorphisms [SNP] [overall 18.6%] among both examined groups [X2 test, P>0.05] indicated that this SNP should be considered as an unrelated mutation to artemisinin resistance. In contrast, S769N mutation was not detected in unexposed isolates; however, it was found in 2.6% [5/191], four years after introduction of ACT in this malaria setting. Also, detected SNPs were not significantly frequent in both unexposed and exposed examined isolates [X2 test, P> 0.05]. Investigation in the

copy number of pfatpase6 gene revealed a similar number of copy [n = 1] as in an isolate sensitive to artemisinin.

19**] Eibach et al.**[54] Malaria Journal 2012, Therapeutic efficacy of artemether-lumefantrine for Plasmodium vivax infections in a prospective study in Guyana. A therapeutic efficacy study was conducted using artemether-lumefantrine + primaquine against P. vivax to evaluate a treatment alternative for chloroquine. Methods: From 2009 to 2010, a non-controlled study in two hospitals in Guyana was conducted. A total 61 patients with P. vivax infection were treated with artemether-lumefantrine as a six-dose regimen twice a day for three days with additional 0.25 mg/kg/d primaquine at day 0 for 14 days. Clinical and parasitological parameters were followed on days 0,1,2,3,7,14 and 28 in agreement with WHO guidelines. Plasmodium vivax DNA from eight patients was analysed for pvmdr1, molecular marker of resistance. Results: Artemether-lumefantrine cleared 100% of parasites on day 1, but two patients [3%] had recurrence of parasites on day 28, suggesting relapse. No pvmdr1 Y976F polymorphism was detected. The treatment regimen was well tolerated.

20] **R. Arun et al,**[55] *Int J Pharm Biomed Res* 2011, Simultaneous HPLC-UV method for the estimation of artemether and lumefantrine in tablet dosage form. the development and validation of a simultaneous HPLC UV method for the estimation of artemether and lumefantrine in fixed-dose combination tablets. The method showed to be linear [r2 > 0.999], precise [RSD < 0.43%], accurate [recovery of 99.81% for artemether and 99.54% for lumefantrine], specific and robust. Three batches of artemether and lumefantrine tablets were assayed by the validated method. The artemether contents in the tablets varied from 99.30 to 99.33%, while lumefantrine contents were 99.65 to 99.66%.A simple isocratic RP-HPLC method has been developed for the simultaneous determination of artemether and lumefantrine using a UV detector. The method was validated for accuracy, precision, specificity and linearity. The method has a relatively short run time [6 min] that allows quantifying a large number of samples in routine and quality control analysis of fixed dose combination tablets.

3. AIM AND OBJECTIVE

OBJECTIVE

Before carrying out a study, it's needful to clearly defined, such that the study presents itself as a valuable contribution to the field of study as well as a thoughtful investment of researchers time. Therefore, the rationale for the study being planned deserves a mention.

Rational of selection of drugs:

Artemether[22,25]

- It is an Antimalarial agent used to treat acute uncomplicated malaria.
- It is administered in combination with lumefantrine for improved efficacy.
- The drug work against the erythrocytic stages of P.falciparum by unhibiting nucleic acid and protein synthesis.
- Rapid onset of action and rapid symptomatic relief
- Half life of the Artemether is variable 3-10 hours and its active metabolite-dihydroartemisinin (DHA) half life- <60 min. peak plasma concentration - 2 hours.

Lumefantrine:[25]

- It is administered in combination with Artemether for improved efficacy.
- It is a blood schizonticide active against erythrocytic stages of Plasmodium falciparum.
- It has a much longer half life and clears residual parasites.
- Half life of lumefantrine ~ 4.5 days peak plasma concentration 6 to 8 hr.

Rational of combination drug therapy[23,24]

- Artemisinins are almost 100% effective, but recrudescence rates are high. So usage only in combination with longer acting drug.

- It causes faster parasite clearance than quinine.
- It is safer and better tolerated than quinine.
- Its dosing schedule is simpler.
- Recent evidence indicates higher efficacy and lower mortality.
- Available in fixed dose combination.
- Lumefantrine has been used only in combination with artemether.
- Artemether quickly reduces parasite biomass and resolves symptoms.
- Lumeantrine prevent recrudescence.
- This combination is used in treatment of uncomplicated chloroquine/ multidrug-resistant falciparum malaria.

Rational of selection of dosage form:

For oral, a tablet has performed as the most preferred dosage form for administration of drugs because of the dosage form's ease of administration simple to manufacture and good stability.

Aim and objective of the study:

The aim of the work is to develop a stable, pharmaceutically equivalent, fixed dose combination of Artemether and Lumefantrine fixed dosage form.

The objective of present study is:

- To formulate the fixed dose combination of tablet of antimalarial activity in multi drug resistance falciparum malaria.
- To develop a physic-chemically stable combination fixed dosage form.
- To develop the process and analysis of the formulation.
- To develop a fixed dose combination therapy dosage form that has comparable in vitro dissolution profile as compared to marketed product.
- To evaluate all the parameters of formulation in detail including stability.
- The pharmaceutically equivalent of the developed formulation is studied by using *f1* & *f2* similarity factor.

4. PLAN OF WORK

The scheme of the entire work is listed as follows:

1. Preformulation studies [19]

   Preformulation involves the characterization of a drug's physical, chemical, and mechanical properties in order to choose what other ingredients should be used in the preparation.

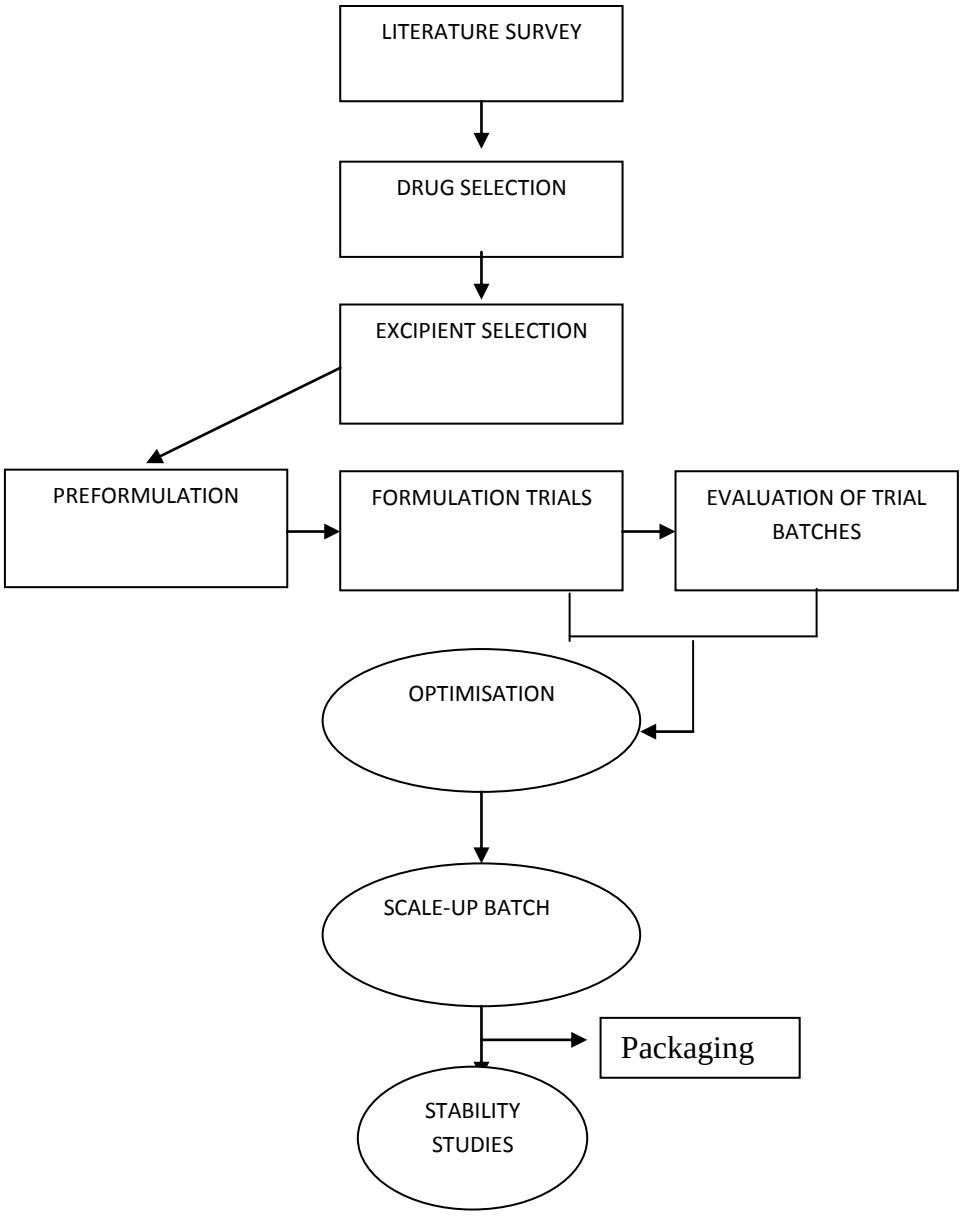
   - Physical observation
   - Bulk density
   - Tapped density
   - Hausner's Ratio
   - Car's Index
   - Particle size distribution
   - Solubility
   - Compatibility studies of drug with various excipients

2. Preparation of tablet blend.
3. Evaluation of Blend
   - Angle of repose
   - Bulk density and tapped density
   - Compressibility index
   - Hausner's Ratio
   - Drug content uniformity
4. Preparation of tablets containing excipients.
5. Evaluation of tablets
   - Tablet appearance
   - Weight Variation
   - Hardness
   - Friability
   - Thickness

- Disintegration test
- Content Uniformity
- In vitro dissolution testing
- Multimedia dissolution studies

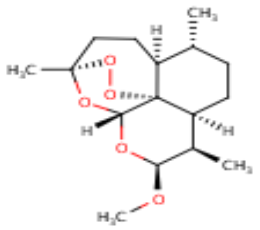
6. Comparison of the optimized formulation with the marketed product.
7. Stability studies of optimized formulation.

NUTSHELL THE PLAN OF WORK WAS AS SHOWN BELOW:



5. DRUG & EXCIPIENT PROFILE

1. ARTEMETHER[22,25,59,60]

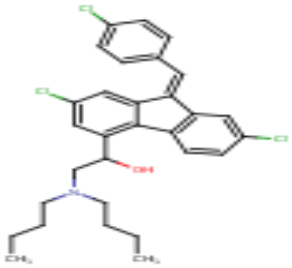
Name	Artemether
Type	small molecule
Description	White Crystalline Powder
Structure	
Synonyms	Dihydroartemisinin methyl ether
IUPAC Name	10-methoxy-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]hexadecane
Categories	▪ Antimalarials ▪ Antiprotozoal Agents ▪ Antimalarial Agents
Weight	Average: 298.3746 Monoisotopic: 298.178023942

Chemical Formula	$C_{16}H_{26}O_5$	
Brand mixtures	**Brand Name**	**Ingredients**
	Coartem	Artemether + lumefantrine
	Riamet	Artemether + lumefantrine
Solubility	Insoluble in water. Soluble in oil.	
Indication	Artemether and lumefantrine combination therapy is indicated for the treatment of acute uncomplicated malaria caused by *Plasmodium falciparum*, including malaria acquired in chloroquine-resistant areas. May also be used to treat uncomplicated malaria when the *Plasmodium* species has not been identified. Indicated for use in adults and children greater than 5 kg.	
Pharmacodynamics	In the body, artemether is metabolized into the active metabolite metabolite dihydroartemisinin. The drug works against the erythrocytic stages of *P. falciparum* by inhibiting nucleic acid and protein synthesis. Artemether is administered in combination with lumefantrine for improved efficacy. Artemether has a rapid onset of action and is rapidly cleared from the body. It is thought that artemether provides rapid symptomatic relief by reducing the number of malarial parasites. Lumefantrine has a much longer half life and is believed to clear residual parasites.	
Mechanism of action	Involves an interaction with ferriprotoporphyrin IX ("heme"), or ferrous ions, in the acidic parasite food vacuole, which results in the generation of cytotoxic radical species. The generally accepted mechanism of action of peroxide antimalarials involves interaction of the peroxide-containing drug with heme, a hemoglobin degradation byproduct, derived from proteolysis of hemoglobin. This interaction is believed to result in the formation of a range of potentially toxic oxygen and carbon-centered radicals.	
Absorption	Food increases absorption.	

Protein binding	Artemether, 95.4%; Dihydroartemisinin, 47-76%	
Metabolism	Rapidly metablized to its active metabolite, dihydroartemisinin.	
Toxicity	Common side effects of combination artemether/lumefantrine therapy in adults include headache, anorexia, dizziness, and asthenia. Common side effects in children include pyrexia, cough, vomiting, anorexia, and headache. Possible serious adverse effects include QT prolongation, bullous eruption, urticaria, splenomegaly (9%), hepatomegaly (adults, 9%; children, 6%), hypersensitivty reaction, and angioedema.	
Affected organisms	▪ Plasmodium	
Manufacturers	▪ Novartis pharmaceuticals corp	
State	Solid	
Experimental Properties	**Properties**	**Value**
	Melting Point	86-90
	logP	3.53
Predicted Properties	Properties	Value
	water solubility	4.57e-01 g/l
	logP	3.02
	logP	3.48

	logS	-2.8
	pKa (strongest basic)	-3.9
	physiological charge	0
	hydrogen acceptor count	5
	hydrogen donor count	0
	polar surface area	46.15
	rotatable bond count	1
	refractivity	74.66
	polarizability	32.12
Drug Interaction	Concurrent administration of artemisinin compounds with terfenadine Astemizole. patient should avoid the following: grapefruit juice; antiarrhythmics, such as amiodarone, disopyramide, flecainide, procainamide and quinidine; antibacterials, such as macrolides and quinolones; all antidepressants; antifungals such as imidazoles and triazoles; terfenadine; other antimalarials; all antipsychotic drugs; and beta blockers, such as metoprolol and sotalol. However, there is no evidence that co-administration with these drugs would be harmful	
Food Interaction	▪ Grapefruit juice may increase the toxicity of artemether and lumefantrine by inhibiting their metabolism. ▪ Take with food as food increases the absorption of artemether and lumefantrine.	

2. LUMEFANTRINE[59,60]

Name	**Lumefantrine**	
Type	Small molecule	
Description	Yellow Crystalline Powder	
Structure		
Synonyms	Benflumetol	
IUPAC Name	2-(dibutylamino)-1-[(9Z)-2,7-dichloro-9-[(4-chlorophenyl)methylidene]-9H-fluoren-4-yl]ethan-1-ol	
Categories	▪ Antimalarials ▪ Antimalarial Agents	
Weight	Average: 528.94 Monoisotopic: 527.154947772	
Chemical Formula	$C_{30}H_{32}Cl_3NO$	
Brand mixtures	**Brand Name**	**Ingredients**
	Coartem	artemether + lumefantrine

Solubility	Insoluble in water. Soluble in oil.
Indication	Lumefantrine and artemether combination therapy is indicated for the treatment of acute uncomplicated malaria caused by *Plasmodium falciparum*, including malaria acquired in chloroquine-resistant areas. May also be used to treat uncomplicated malaria when the *Plasmodium* species has not been identified. Indicated for use in adults and children greater than 5 kg.
Pharmacodynamics	Lumefantrine is a blood schizonticide active against erythrocytic stages of *Plasmodium falciparum*. It is thought that administration of lumefantrine with artemether results in cooperate antimalarial clearing effects. Artemether has a rapid onset of action and is rapidly cleared from the body. It is thus thought to provide rapid symptomatic relief by reducing the number of malarial parasites. Lumefantrine has a much longer half life and is believed to clear residual parasites.
Mechanism of action	The exact mechanism by which lumefantrine exerts its antimalarial effect is unknown. However, available data suggest that lumefantrine inhibits the formation of β-hematin by forming a complex with hemin and inhibits nucleic acid and protein synthesis.
Absorption	Food increases absorption.
Protein binding	99.7% bound
Metabolism	Extensively metabolized in the liver primarily by cytochrome P450 3A4. The major metabolite found in plasma is desbutyl-lumefantrine.
Toxicity	Common side effects of combination artemether/lumefantrine therapy in adults include headache, anorexia, dizziness, and asthenia. Common side effects in children include pyrexia, cough, vomiting, anorexia, and headache. Possible serious adverse effects include QT prolongation, bullous eruption, urticaria, splenomegaly (9%), hepatomegaly (adults, 9%; children, 6%), hypersensitivty reaction, and angioedema.

Affected organisms	Plasmodium	
Manufacturers	Novartis pharmaceuticals corp.	
State	solid	
Predicted Properties	**Properties**	**Value**
	water solubility	3.09e-05 g/l
	logP	8.34
	logP	9.19
	logS	-7.2
	pKa (strongest acidic)	14.1
	pKa (strongest basic)	9.78
	physiological charge	1
	hydrogen acceptor count	2
	hydrogen donor count	1
	polar surface area	23.47
	rotatable bond count	10
	refractivity	160.81

	polarizability	60.69
Drug Interaction	It should not be given with drugs metabolized by CYP2D6 (metoprolol, neuroleptics, tricyclic antidepressants, etc) or drugs which prolong QTc interval.	
Food Interaction	▪ Grapefruit juice may increase the toxicity of artemether and lumefantrine by inhibiting their metabolism. ▪ Take with food as food increases the absorption of lumefantrine and artemether.	

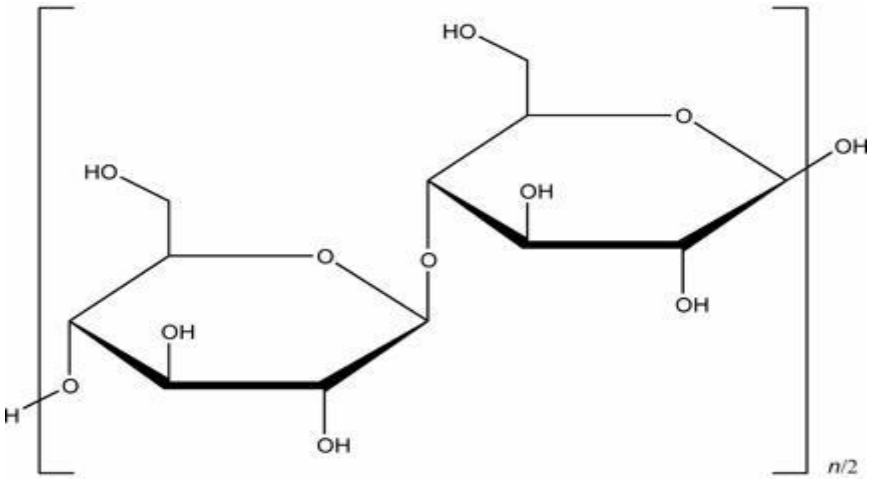
EXCIPIENTS PROFILE[8,11]

Micro Crystalline Cellulose

Non Proprietary Names

BP	:	Microcrystalline Cellulose
JP	:	Microcrystalline Cellulose
PhEur	:	Cellulose, Microcrystalline
USP-NF	:	Microcrystalline Cellulose
Synonyms	:	Avicel PH; Celex; Cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; ethispheres .

Structural Formula:



Description: Microcrystalline cellulose is purified partially depolymerised cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Chemical Name	:	Cellulose
Empirical Formula	:	$(C_6H_{10}O_5)_n$ where n = 220
Molecular Weight	:	36000

Functional Category:

Adsorbent, Suspending agent, tablet and capsule, diluents, tablet disintegrant.

Stability and Storage Conditions:

Microcrystalline cellulose is a stable through hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Microcrystalline cellulose is a incompatible with strong oxidizing agents.

Applications

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluents in oral tablet and capsule formulations where it is used in both wet granulation and direct-compression processes. In addition to its use as a binder/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

MAGNESIUM STEARATE

Synonyms	Stearic acid magnesium salt, magnesium salt, magnesium octadecanoate
Description	If is a fine, white, precipitated of milled, impalpable powder of low bulk density, having a faint odor of stearic acid & a characteristic taste.
Structural Formula	$[CH_3(CH_2)_{16}COO]_2Mg$
Empirical Formula & Molecular Weight	$C_{36}H_{70}MgO_4$; 591.34
Solubility	It is insoluble in water, ethanol & ether, slightly soluble in warm benzene & warm ethanol
Functional categories	Table & capsule lubricant
Melting point	117- 150°C
Density (bulk)	$0.159 gm/cm^3$
Density (tapped)	$0.286 gm/cm^3$
Stability and storage conditions	Should be stored in well-closed container in a cool, dry place. It is stable compound.
Incompatibilities	Incompatible with strong oxidizing agents, strong acids, alkalis & iron salts. It cannot be used in products containing aspirin, some vitamins, & most alkaloidal salts.

Safety	It is nontoxic. However, oral consumption of large quantity may result in some laxative effect or mucosal irritation.
Applications	Used in cosmetics, food & pharmaceutical formulations and as a lubricant in capsule & table at concentration between 0.25-5.0%.

COLLOIDAL SILICONE DIOXIDE (AEROSIL)

Nonproprietary Names

BP	:	Colloidal anhydrous silica
PhEur	:	Silica colloidalis anhydrica
USPNF	:	Colloidal silicon dioxide
Synonyms	:	colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride and silicon dioxide fumed
Chemical Name	:	Silica
Molecular Weight	:	60.08
PH	:	3.5-5.5
Loss on drying	:	$\leq 2.5\%$
Density (bulk)	:	$0.029 – 0.042$ gm / cm^3
Functional Category	:	SiO_2 is an Adsorbent, anticaking agent, emulsion stabilizer, glident, suspending agent, tablet disintegrant, thermal stabilizer, and viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area gives desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tabletting.

Description:

Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, and non-gritty amorphous powder.

Stability and Storage Conditions:

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0-7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well-closed container. Some grades of colloidal silicon dioxide have hydrophobic surface treatments that greatly minimize their hygroscopicity.

Incompatibilities:

Incompatible with diethylstilbestrol preparation

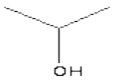
Safety:

It is widely used in oral and topical pharmaceutical formulation and is generally regarded as a nontoxic and nonirritant material. Intraperitonial and subcutaneous injection may produce local tissue radiations and or granulomas.

Applications:

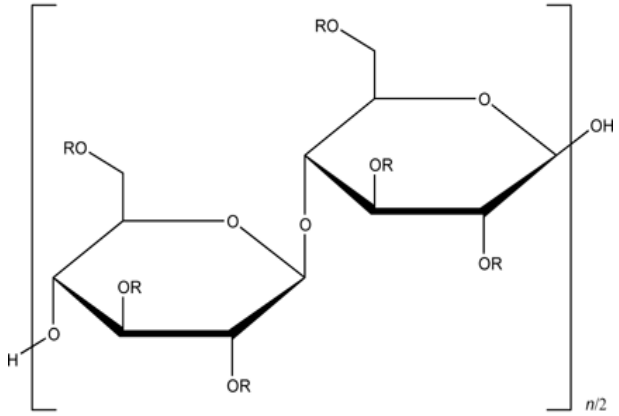
It is widely used in pharmaceuticals, cosmetics, and food products. It is mainly used as a glidant for tableting.

ISO PROPYL ALCOHOL[29]

Nonproprietary names	:	BP - isopropyl alcohol JP – isopropanol Ph EUR – alcohol isopropylicus
Empirical formula	:	C3H8O
Chemical name	:	Propan-2-ol
Structural formula	:	
Molecular weight	:	60.1 g/mol
Description	:	It is a clear color less, mobile, volatile, flammable,liquid with a characteristic spirituous odour resembling that of amixture of ethanol and acetone, it has a slight bitter taste.
Functional categories	:	Disinfectant and solvent
Solubility	:	Miscible with benzene, chloroform, Ethanol (95%), ether and water
Melting point	:	88.5°C
Flash point	:	11.7°C (closed cup) and 10° C (open cup)
Moisture content	:	0.1-13 %w/w; commercial grades-13 %w/w.
Stability and storage	:	stored in well-closed container in a cool and dry place
Applications	:	Used in lotions, used as a solvent both for tablet film coating, Granulation and topical disinfectant
Incompatibilities	:	Incompatible with oxidizing agents such as hydrogen-per-oxide and nitric acid, which cause decomposition. IPA may be salted out from aqueous mixtures by the addition of sodium chloride and other salts or by the addition of sodium hydroxide.

HYDROXYPROPYL CELLULOSE

Chemical structure:



Nonproprietary Name

BP **:** Hydroxypropyl cellulose

Ph .Eur **:** Hydroxypropyl cellulosum

USP **:** Hydroxypropyl cellulose

Synonyms **:** Cellulose Hydroxypropyl Ether; E463; Hyprolose; Klucel; Methocel; Nisso HPC ; Oxypropylate Cellulose.

Description **:** Hydroxypropyl cellulose is a white to slightly yellow-colored odorless and tasteless powder. It may contain not more than 0.6% of silica some other suitable anticaking agent. Hydroxypropyl cellulose is commercially available in number of different grades which have different solution viscosity.

Solubility : Hydroxypropyl cellulose is freely in water below 38 c forming a smooth, clear, colloidal solution. It is soluble in cold or hot polar organic solvent such as; dimethyl formamide; dimethyl sulfoxide ethanol.

Application : Hydroxypropyl cellulose is widely used oral and tropical pharmaceutical formulation. In oral product, hydroxypropyl cellulose is primarily used in tableting as binder, film-coating and extended release matrix

Use Concentration (%)

Extended release matrix 15-35

Tablet binder 2-6

Tablet film-coating 5

Incompatibilities: Hydroxypropyl cellulose is incompatibilities with substituted phenol derivatives such as methylparaben propylparaben

Stability : Hydroxypropyl Cellulose powder is stable material although it is hygroscopic after drying.

Storage Condition: Hydroxy propyl Cellulose powder should be stored in well closed container in cool, dry, place.

CROSCARMELLOSE SODIUM

Nonproprietary Names:

BP : Croscarmellose Sodium

JP : Croscarmellose Sodium

PhEur : Croscarmellose Sodium

USP-NF : Croscarmellose Sodium

Synonyms : Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

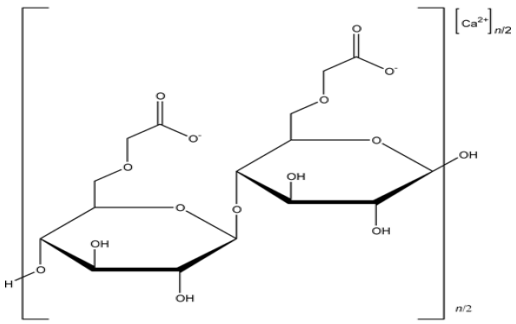
Chemical Name and CAS Registry Number:

Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811- 65-7]

Empirical Formula and Molecular Weight:

Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium.

Structural Formula:



Functional Category:

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology:

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules,(1,2) tablets,(3–13) and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.(11,12) Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Use Concentration: (in %)

Disintegrant in capsules 10–25

Disintegrant in tablets 0.5–5.0

Description:

Croscarmellose sodium occurs as an odorless, white or grayish white powder.

Typical Properties:

Acidity/alkalinity pH = 5.0–7.0 in aqueous dispersions.

Bonding index 0.0456

Brittle fracture index 0.1000

Density (bulk) 0.529 g/cm3 for Ac-Di-Sol

Stability and Storage Conditions:

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 308C for 14 months.(9) Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Safety:

Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems. In the UK, croscarmellose sodium is accepted for use in dietary supplements. The WHO has not specified an acceptable daily intake for the related substance carboxymethylcellulose sodium, used as a food additive, since the levels necessary to achieve a desired effect were not considered sufficient to be a hazard to health.

POLYSORBATE 80

Synonym **:** TWEEN 80; Polyoxyethylene 20 sorbitan monooleate; Polyethylene oxide sorbitan mono-oleate; Polyoxyethylene sorbitan monooleate; Polyoxyethylene sorbitan oleate; Sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl) derivatives; Sorethytan (20) monooleate

Chemical Name **:** Sorbitan, monooleate polyoxyethylene derivative.

Physical state and appearance: Liquid. (Oily liquid.)

Odor **:** fatty (Slight.)

Color **:** Clear Amber. Yellow.

pH (1% soln/water): 7 [Neutral.]

Boiling Point **:** >100°C (212°F)

Melting Point **:** -20.556°C (-5°F)

Specific Gravity **:** 1.06 - 1.10 (Water = 1)

Solubility **:** Easily soluble in cold water, hot water. Soluble in methanol. Soluble in Toluene, alcohol, cottonseed oil, corn oil, Ethyl Acetate. Insoluble in mineral oil..

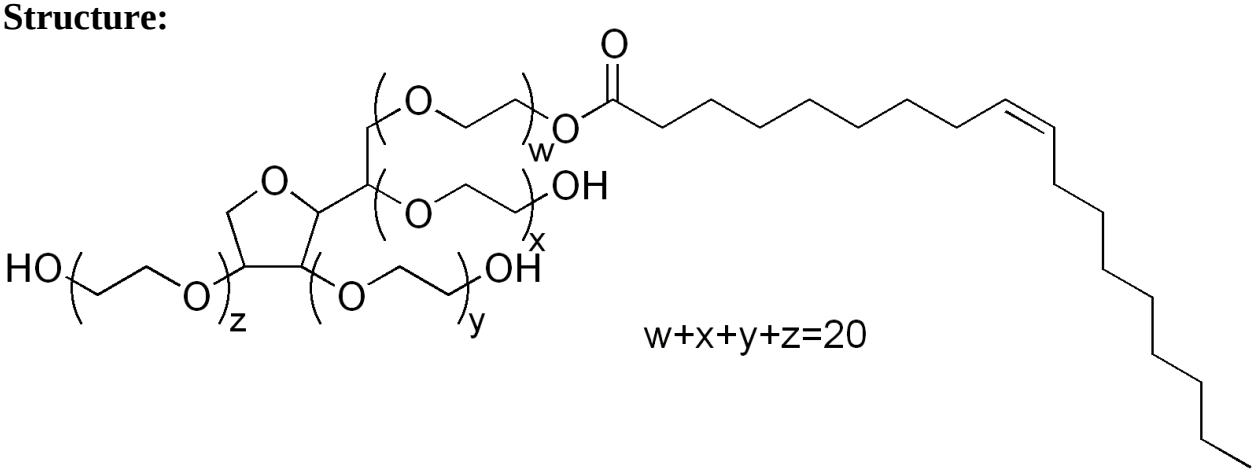
Incompatibility with various substances:

Reactive with oxidizing agents.

Corrosivity:

Non-corrosive in presence of glass, of stainless steel(304), of stainless steel(316).

Structure:



Food use:

Polysorbate 80 is used as an emulsifier in foods, particularly in ice cream. Here, polysorbate is added to up to 0.5% (v/v) concentration and makes the ice cream smoother and easier to handle, as well as increasing its resistance to melting.[4] Adding this substance prevents milk proteins from completely coating the fat droplets. This allows them to join together in chains and nets, which hold air in the mixture, and provide a firmer texture that holds its shape as the ice cream melts.

Medical use:

Polysorbate 80 is an excipient that is used to stabilize aqueous formulations of medications for parenteral administration, and used as an emulsifier in the manufacture of the popular anti-arrhythmic amiodarone.[5] It is also used as an excipient in some European and Canadian influenza vaccines.[6] It is also used in the culture of Mycobacterium tuberculosis in Middlebrook 7H9 broth.

Laboratory use:

Some mycobacteria contain a type of lipase (enzyme that breaks up lipid molecules). When added to a mixture of Tween 80 and phenol red, they cause the solution to change colour, so this is used as a test to identify the phenotype of a strain or isolate.

Molecular formula	$C_{64}H_{124}O_{26}$
Molar mass	1310 g/mol
Appearance	Amber colored viscous liquid
Density	1.06–1.09 g/mL, oily liquid
Boiling point	> 100°C
Solubility in water	Very soluble
Solubility in other solvents	soluble in ethanol, cottonseed oil, corn oil, ethyl acetate, methanol, toluene
Viscosity	300–500 centistokes (@25°C)
Main hazards	Irritant
Flash point	113 °C

6. MATERIALS AND EQUIPMENTS

API, excipients and equipments used for the development of formulation:

S.No.	Materials	Suppliers
1	Artemether	Mangalam drugs Pvt
2	Lumefantrine	Mangalam drugs Pvt
3	Hydroxyl propyl cellulose	Welming pharmaceuticals, India
4	Polysorbate 80	Welming chemicals,india
5	Iso propyl alcohol	Loba chemie.,pvt ltd,. Mumbai
6	Microcrystalline cellulose	Welming chemicals, India
7	Croscarmelose sodium	S.D.Fine-Chemi.,Pvt Ltd., Mumbai
8	Aerosil	Amaratal & Co., Chennai
9	Magnesium stearate	Loba chemie., Pvt. Ltd., Mumbai

Equipments used for formulation and analysis purpose

S.No.	Equipments	Manufacturer
1	Tablet compression machine - 12 station (Single Rotary)	CIP Machinery
2	Die & Punch	CIP Machinery
3	Planetary Mixer	Kenwood
4	Hot air oven	Lab India
5	Dissolution apparatus(usp)	Electro Lab
6	Electromagnetic sieve shaker (ESM- 8)	Electrolab
7	Tablet Hardness tester (8M)	Dr.Schleuniger,pharmaton, USA
8	PH meter	Lab India
9	Reverse phase High Pressure Liquid chromatograph (HPLC)	Shimadzu
10	UV visible spectrophotometer	Perkin Elmer
11	Electronic Weighing Balance	Essac Teraoka Ltd (Japan)
12	Digital high precision balance (single pan)	Mettler – Toledo (switzerland)
13	Disintegration tester	Electro Lab
14	Roche Friabilator USP	Electro Lab
15	Mechanical stirrer	Remi Motors, Bombay.
16	Tabbed density tester	Electro lab
17	Bulk density apparatus	Electro lab
18	Stability chambers	Thermo lab, Mumbai
19	Sieves (A.S.T.M)	Rajdhani
20	Digital Vernier Calipers CD-6 inch CSX	Mitutoyo Corp, Japan
21	Blister Packing Machine	Precision Gears Ltd.IMA,Italy
22	Humidity Chamber HTC 3003	Thermolab

7. EXPERIMENTAL WORK

PREFORMULATION STUDY[19]

Preformulation studies can be defined as an investigation of physical and chemical properties of active pharmaceutical ingredient, alone and in combination with excipients. It is the first step in rational development of a formulation or dosage form.

The objective of Preformulation studies is to generate information useful to the formulator in developing stable and bioequivalent dosage form. Obviously the types of information needed will depend on the dosage form to be developed.

Evaluation of Drug:

It is the first step in rationale development of a formulation or dosage form of a drug substance. Preformulation studies can be defined as an investigation of physical and chemical properties of active pharmaceutical ingredient, alone and in combination with excipients.

Scope:

The use of Preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product and at same time provides the basis for optimization of the drug product quality.

The formal preformulation study is start at the point after biological screening. When a decision is made for the further development of the compound in clinical trials - embarking on a formal program.

Preliminary activities in this drug product development project started with a comprehensive review of authoritative reference books on the pharmaceutical and analytical parameters and attributes of the chosen drug.

The preformulation scientist must consider the following:

- Available Pharmacokinetic data.
- Anticipated dose
- Supply situation and development schedule.
- Nature of the information the formulator should have or would like to have.

The above considerations will offer the preformulation scientist some guidelines in deciding the types and the urgency of the studies that need the attention.

Preformulation studies:

1. Evaluation of drug
    - Description
    - Melting point
    - Solubility
    - Water content by Loss on Drying
    - Hygroscopic Nature

2. Differential scanning calorimetry – to analyse the incompatibility of the drug with the polymer

3. Physical evaluation of the granules

    - Bulk Density
    - Tapped density
    - Carr’s Index

- Haunser’s Ratio
- Angle of Repose

4. Evaluation of the formulated tablet

- Friability
- Hardness
- Thickness
- Uniformity of weight
- Swelling and erosion study
- Assay
- In vitro drug release
- Stability Study
- Release kinetics

Description:

- About 1g Artemether and lumefantrine of sample is taken in a dry petridish and the sample is observed for compliance against the specification.
  Observation: Artemether – white crystalline powder. Lumefantrine – yellow crystalline powder

Identification of pure drug: Identification of artemether and lumefantrine is carried out by Infra Red Absorption Spectrophotometry.

Melting Point Determination:[29]

Melting Point Determination of Artemether

Sample	Melting point (˚C)		Reference Range (˚C) (IP)
	1	2	
Artemether	86-88	86-89	86 – 90

Table No.24

Melting Point Determination of Lumefantrine:

Sample	Melting point (˚C)		Reference Range (˚C) (IP)
	1	2	
Lumefantrine	128 - 130	128 - 131	128 – 132

Table No.25

The melting point of the sample agreed with the literature value of 86-90˚C as stated in the IP, further confirming the sample as Artemether and also ascertaining its purity.

The melting range of the sample was 128–130˚C and this agreed with the literature value of 128–132˚C. as stated in the USP SALMOUS Standard.

Organoleptic properties: The color, odor and taste of the drug were recorded using descriptive terminology.

Organoleptic properties	Artemether	Lumefantrine
Colour	white crystals	yellowish powder
Odour	Odourless	Odourless
Taste	Slightly Bitter	Bitter
Microscopic examination	Crystalline powder	Amorphous powder

Table No.26

Solubility Studies:[22]

The spontaneous interaction of two or more substance to form a homogeneous molecular dispersion is called as solubility. The solubility of Artemether and Lumefantrine was studied in various solvents. The solubility profiles of Artemether and Lumefantrine in various solvents are shown in the Table. The approximate solubility's of substances are indicated by the descriptive
terms in the accompanying table.

Descriptive term	Parts of solvent required for 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly Soluble	From 100 to 1000

Table No.27

Solubility Profile of Artemether:

S. No	Solvent	Solubility
1	Distilled water	Insoluble
2	PBS (pH 6.8)	Soluble
3	Acetonitrile	Soluble
4	0.1 N HCL	Soluble
5	Ethanol	Soluble
6	Dichloromethane	Soluble

Table No.28

Solubility Profile of Lumefantrine:

S. No	Solvent	Solubility
1	Distilled water	Insoluble
2	PBS (pH 6.8)	Soluble
3	Acetonitrile	Soluble
4	0.1 N HCL	Soluble
5	Ethanol	Soluble
6	Dichloromethane	Soluble

Table No.29

Determination of particle size:[17]

Sieve analysis:

The main aim of sieve analysis is to determine the different size of drug particles present. A series of standard sieve were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieves with smaller pore size (greater sieve number towards the bottom).

Procedure:

A series of sieves were arranged in the order of their decreasing pore diameter (increasing sieve number) i.e. sieve number 20, 30, 40, 60, 100, and 200. 100 grams of drug was weighed accurately and transferred to sieve number 20 which were kept on top. The sieves were shaken for about 5-10 minutes on mechanical sieve shaker having bottom tap motion. Then the drug retained on each sieves was taken, weighed separately and amount retained was expressed in terms of percentage.

Observation of particle size of Artemether:

Sieve No.	Weight retained (gm)	% Retained	Cumulative % Retained	% passed
20	0.3282	1.9912	1.9912	98.0088
40	6.180	37.5201	39.5113	60.4887
60	8.3150	50.4495	89.9608	10.0392
100	0.3409	2.0683	92.0291	7.9709
Base plate	0.1580	0.9586	--	--

Table No.30

Observation of particle size of Lumefantrine:

Sieve No.	Weight retained (gm)	% Retained	Cumulative % Retained	% passed
20	0.381	2.1404	2.1404	97.8596
40	1.432	8.0449	10.1853	89.8147
60	5.890	33.089	43.2743	56.7257
100	8.931	50.174	93.4483	6.5517
Base plate	1.233	6.9269	--	--

Table No.31

Determination of Bulk density: [12]

Bulk density is defined as a mass of a powder divided by the bulk volume. A sample powder of Active pharmaceutical ingredient was introduced in 100 ml graduated cylinder. The volume of the material was noted on graduated cylinder. The bulk density was calculated by the formula given below.

Bulk density (ρ_0) = M/Vo

Where, M = mass of the powder

Vo = volume of the powder

Determination of Tapped Density: [12]

The powder sample under test was screened through sieve no. 18 and the weight of sample equivalent to 10 g was filled in 100 ml graduated cylinder. The mechanical tapping of the cylinder was carried out at a rate of 300 drops per minute for 500 times from 3" height and the tapped volume Vf was noted.

The tapped density was calculated in gm/ cm^3 by the formula,

Tapped density (ρ_t) = M/Vf

Where, M = weight of sample powder taken

Vf = tapped volume

Determination of Flow properties:[19]

Hausner's Ratio:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner's Ratio = Tapped density / Bulk density

Compressibility index (Carr's indices):

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30% is defined as the free flowing material.

$$Ci = \frac{(V0 - Vf) \times 100}{V0}$$

Compressibility index specifications

% Comp. Index	Properties	Hausner's ratio
≤10	Free flowing	1.00 – 1.11
11 -15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very poor	1.46 – 1.59
≥38	Extremely poor	>1.60

Table No.32

Angle of repose:

It is the maximum angle that can be obtained between the freestanding surface of the granules heap and the horizontal plane.

$$\tan \theta = h/r$$

If the angle of repose is less than 30º then the granules is considered to be free flowing.

Flow properties and corresponding Angle of Repose:

Angle of Repose (in degrees)	Flow property
25 – 30	Excellent
31 – 35	Good
36 – 40	Fair – Aid not required
41 – 45	Passable – May hang up
46 – 55	Poor – Mast agitate, vibrate
56 – 65	Very poor
>66	Very. Very poor

Table No.33

Observation of Density and Flow parameter:

Raw Material	Density (g / ml)		Flow properties		
	Bulk	Tapped	Carr's index	Hausner's ratio	Angle of Repose
Artemether	0.3667	0.6875	46.661	1.8748	34.18
Lumefantrine	0.612	0.760	19.41	1.24	36.17

Table No.34

Conclusion: The above observation indicates that Artemether and Lumefantrine drug has very poor flow properties.

Calibration Curve:

Artemether:[25]

50mg of pure Artemether was weighed and made up to 100ml with methanol. 5ml of the Artemether stock solution above was added to corresponding volumes of the prepared Artemether solution and made up to the 25ml mark in a 25ml volumetric flask with the mobile phase giving concentrations of 0.044, 0.048, 0.052, 0.056 and 0.060%w/v. The solutions were injected using indometacin at a concentration of 0.00008%w/v as an external standard.

Concentration (%W/V)	Average peak area ratio
0.002240	0.0616
0.004480	0.1268
0.008960	0.2246
0.013440	0.3188
0.017920	0.4094
0.022400	0.5072
0.026880	0.6087

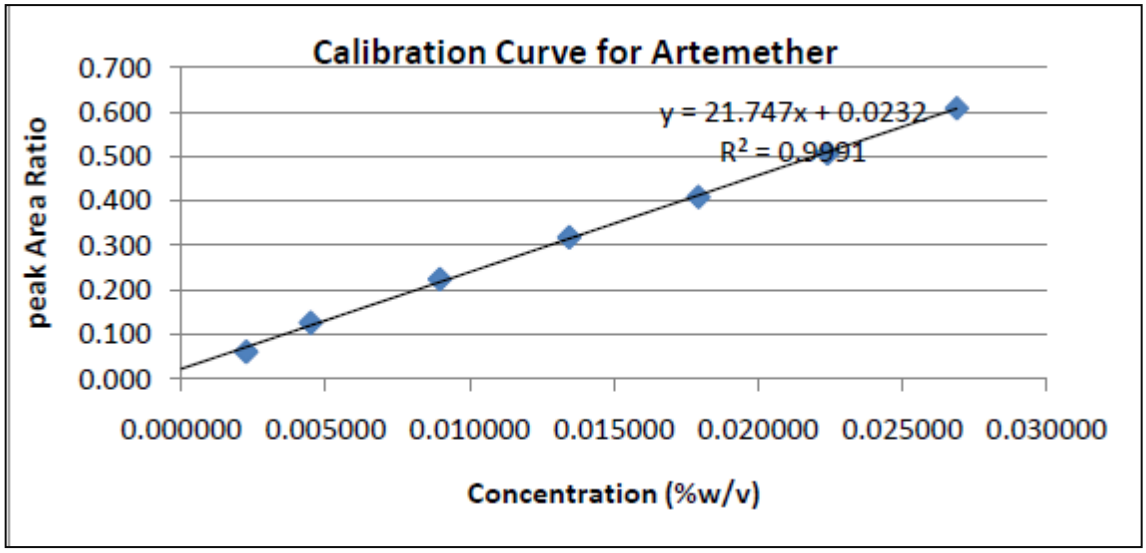


Fig.No.7

Parameters of Calibration Curve	Value
Range	0.002240%w/v - 0.026880%w/v
Slope	21.747
Intercept	0.0200 ± 0.0050
R^2	0.9991

Calibration Curve:

Lumefantrine[29]

Approximately 20mg of Lumefantrine was accurately weighed and dissolved with 0.1M methanolic HCl to the 200ml mark in a volumetric flask. From this stock solution, solutions with concentrations of 0.0008, 0.0012, 0.0016, 0.0020, 0.0024 and 0.0028%w/v were prepared by serial dilution. The absorbances of these solutions at 335nm were obtained with 0.1M methanolic HCl as blank and used in the plotting of a calibration curve.

Conc. (% w / v)	Average Absorbance
0.0008	0.265
0.0012	0.392
0.0017	0.536
0.0021	0.665
0.0025	0.790

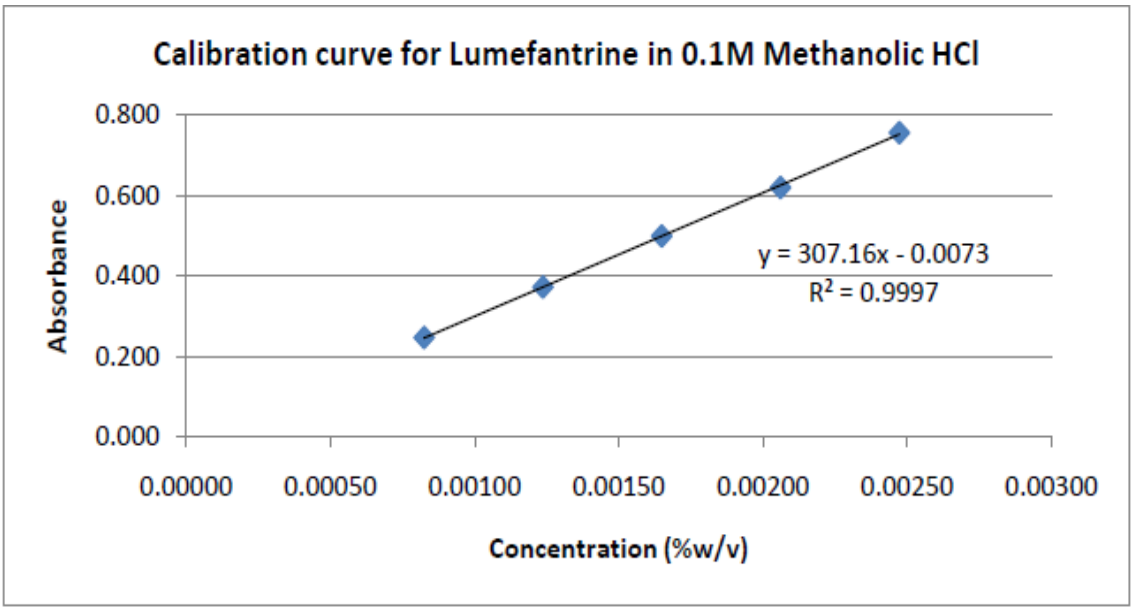


Fig.No.8

Calibration Curve Parameters	Value
Range	0.0008%w/v – 0.0028%w/v
Slope	307.16 ± 2.90
Intercept	0.0073 ± 0.0054
R^2	0.9997

Chromatogram of Artemether for determining λ_{max}:[32,33]

λ_{max} of Artemether – 254 nm

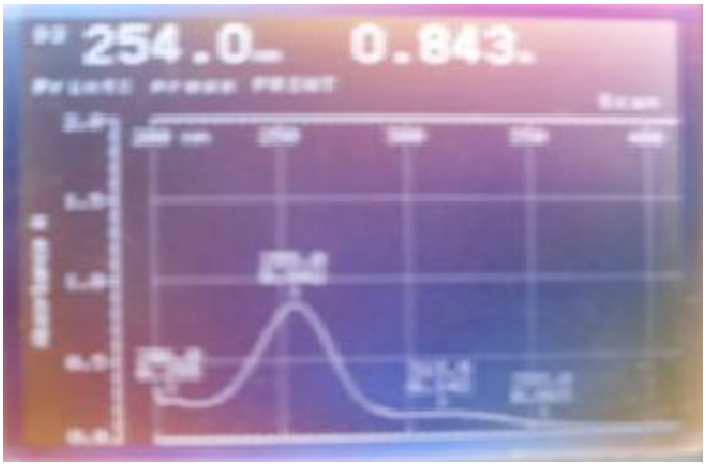


Fig No.9

Chromatogram of Lumefantrine for determining λ_{max}:

$\lambda_{max\ of}$ Lumefantrine– 335 nm

Fig. No.10

FTIR Studies

IR spectra for drug, and powdered tablets were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets. One of the requirements for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work, a study was carried out by using infrared spectrophotometer to find out if there is any possible interaction between the drug and excipients. Weighed amount of drug (3mg) was mixed with 100 mg of potassium bromide (dried at 40-50°C). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000-400 cm^{-1} in IR spectrophotometer.

DRUG-EXCIPIENT COMPATIBILITY STUDY:

In this study the active pharmaceutical ingredient and excipients (different type) are mixed and stored at different conditions for variable time periods.

The physical properties (colour change) were monitored regularly. The change in color in any mixture was the basis for disregarding from study.

Different ratios of Drug and excipient taken for Compatibility Study

Name of the Excipients	Ratio	Initial (0 days)	Final observation		Conclusion
			40 ° C / 75 % RH		
			2nd week	5th week	
Artemether+ Lumefantrine	1:1	Yellow Crystalline powder	Yellow crystalline powder	Yellow crystalline powder	Compatible
AL + MCC	1:1	Yellow crystalline powder	Yellow crystalline powder	Yellow crystalline powder	Compatible
AL + Mg. Stearate	1:1	Yellow crystalline powder	Yellow crystalline powder	Yellow crystalline powder	Compatible
AL + Aerosil	1:1	Yellow crystalline powder	Yellow crystalline powder	Yellow crystalline powder	Compatible
AL + HPC	1:1	Yellow amorphous powder	Yellow amorphous powder	Yellow amorphous powder	Compatible
AL + Isopropyl alcohol	1:1	Yellow amorphous powder	Yellow amorphous powder	Yellow amorphous powder	Compatible
AL + CCS	1:1	Yellow crystalline powder	Yellow crystalline powder	Yellow anhydrous powder	Compatible
AL + Polysorbate 80	**1:1**	Yellow amorphous powder	Yellow amorphous powder	Yellow anhydrous powder	Compatible

Table No.35

INNOVATOR CHARACTERIZATION

Brand Name	**:**	Coartem
Strengths available	:	20 mg + 120 mg
Innovator product information		
Product information	**:**	Coartem – Tablets (Artemether 20 mg+ Lumefantrine 120mg)
Route of administration	:	Oral
Dosage form	:	Tablet
Colour	:	Yellow
Shape	:	Round
Average weight of 10 tablets	:	2.40 g (240 mg / tab)
Average thickness of 10 tablets	:	3.12 mm
Average Diameter of 10 tablets	:	9.5 mm
Description	**:**	Yellow Colored, un-coated round tablet.
Package description	:	24 tablets in 1 blister pack
Storage conditions	:	Store at or below 25°C (77°F)
Manufacturer	:	NOVARTIS

FORMULATION DEVELOPMENT

PROCESS DEVELOPMENT:

The process for formulation of Artemether and lumefantrine was developed in a systematic way. Trials were taken by wet granulation tabletting process with hydrophilic polymers.

TECHNIQUE SELECTION - WET GRANULATION

Manufacturing procedure:

- **Milling and mixing of drug and excipients**

  The Artemether and lumefantrine active drugs was weighed accurately as mentioned in the formula and was mixed with MCC, part of aerosil and sifted through sieve no #100. The blend containing drug and other raw material were mixed in an octagonal blender for 15 minutes.

- **Preparation of binder solution**

  Weigh HPC RTLF add to required quantity of polysorbate 80 and IPA and stirr for 45mins.

- **Wet massing by the addition of binder solution**

  The above binder solution added to dry mixture to form wet mass.

- **Screening of wet mass**

  The wet mass passed through 12# mesh.

- **Drying of the wet granules**

  The screened wet granules were kept in tray drier at 60ºC.

- **Screening of dry granules**

  The dried granules passed through 20# mesh.

- **Blending of dried granules with diluent and disintegrants**

  Weigh accurately aerosil, Croscarmellose sodium was passed through 40# mesh and add to dried granules and mix for 3mins.

- **Addition of Lubricant to produce free flow powder**

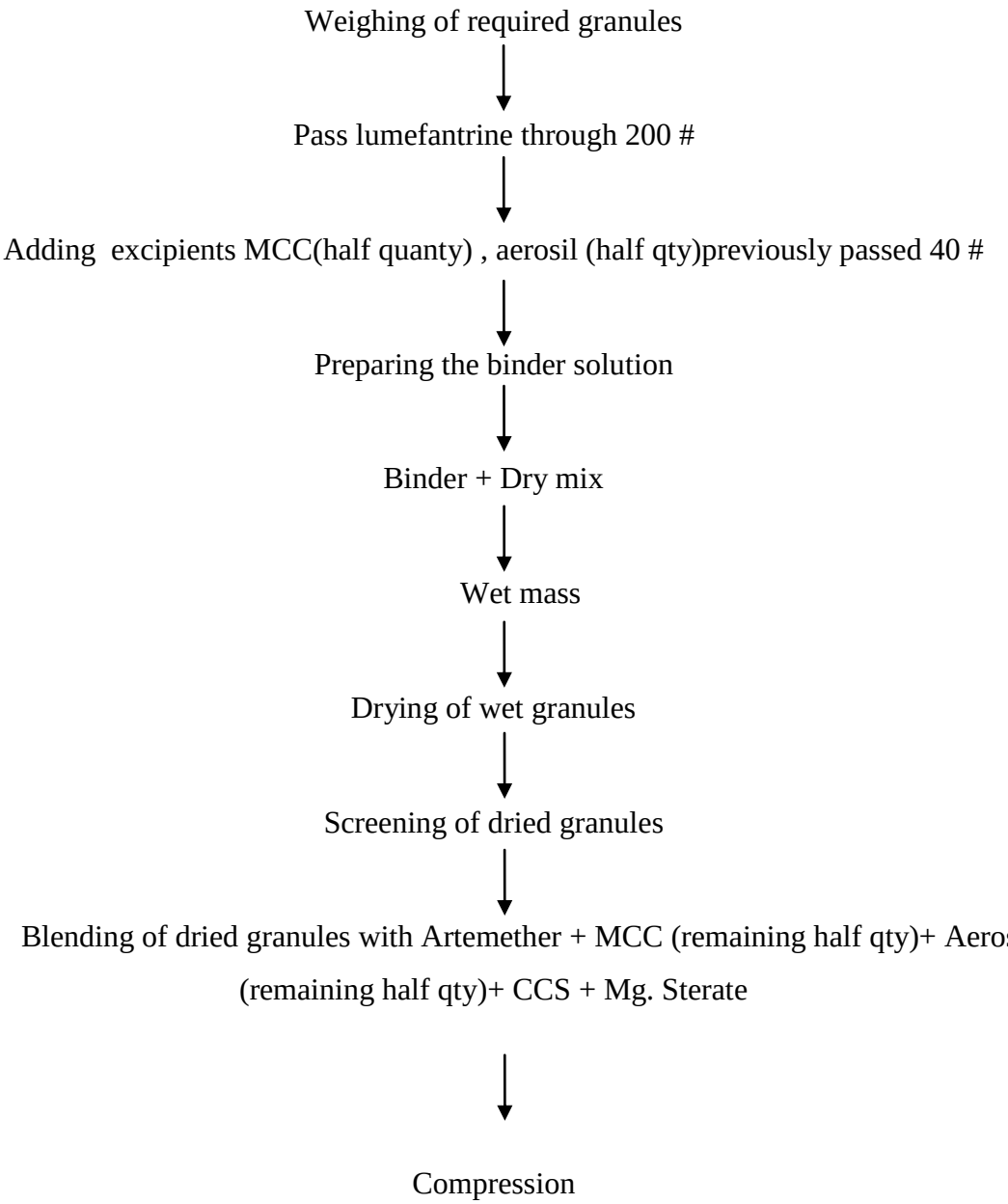
  Previously sifted (sieve no #40) magnesium stearate was added to the granular blend and lubricated for 2mins. Then this final blend was mixed in an octagonal blender for 10 minutes**.**

- **Compression**

  The final lubricated blend was compressed using 19.2 x 11.6mm, oval shaped punch to get the target weight and adequate hardness.

Photo copy of Compressed uncoated tablets

PROCESS FLOW CHART



Different trial formulations:

INGREDIENTS	F1	F2	F3	F4	F5	F6
Lumefantrine	120.00	120.00	120.00	120.00	120.00	120.00
Artemether	20.00	20.00	20.00	20.00	20.00	20.00
Microcrystalline cellulose	84.75	81.5	80.5	78.50	80.50	80.50
Aerosil	5.00	4.75	4.00	3.50	4.00	4.00
Hydroxyl propyl cellulose	0.25	0.75	1.50	2.00	1.50	1.50
Croscarmellose sodium	2.00	4.00	5.00	7.00	-	-
Crospovidone	-	-	-	-	5.00	5.00
Magnesium stearate	6.00	6.00	6.00	6.00	6.00	6.00
Polysorbate 80	2.00	3.00	3.00	3.00	3.00	3.00
Iso propyl alcohol	Qs (80 ml)	Qs (80 ml)	Qs (80 ml)	Qs (80 ml)	Qs (80 ml)	Qs (80 ml)

Trial Batch F5 & F6 = Failure

Table No.36

Punch sets description:

Item	Standards
Upper punch	9.1 mm Flat circular punch with break line
Lower punch	9.1 mm Plain flat circular punch
Dies	Circular (Round)shape

Table No.37

Tablet Parameters as follows:

Parameters	Specification
Description	Yellow, circular, flat, beveledged uncoated tablet having a breakline on oneside and otherside plain.
Theoretical mass of tablet	240.00 mg
Average mass	240.0 mg ± 5.0%
Uniformity of mass	NMT 2/20 individual mass deviate from ± 7.5% of the average mass.
Diameter	9.00 ± 0.10 mm
Thickness	3.00 ± 0.30 mm
Hardness	4 – 5 kg / cm^2
Friability	NMT 1.0 %m/m.
Disintegration time	NMT 15 minutes in water at $37^0 \pm 2^0$C

Table No.38

Parameters for evaluation of designed formulation:

1. Pre-compression parameter evaluation

- **Granules evaluation (Lubricated blend)**
  - Particle size
  - Density

- Loss on drying
- Flow properties
- Compressibility

2. Post-compression parameter evaluation:

- **Tablet evaluation**

    - Description
    - Appearance
    - Weight variation
    - Thickness
    - Hardness
    - Uniformity of weight
    - Friability
    - In Vitro Dissolution Studies (Mathematical model of in vitro dissolution)
    - Assay

3. Accelerated Stability Study:

- Stability study as per ICH Guidelines

Granules evaluation:[22]

Particle size, density, loss on drying (moisture content), flow properties, and compressibility of the granules was determined similar to text characterized in preformulation study.

Particle size determination

Sieving is the most widely used method for measuring particle size distribution because it is inexpensive, simple, and rapid with little variation between operators The procedure involves the mechanical shaking of a sample through a series of successively smaller sieve, and weighing of the portion of the sample retained on each sieve. The type of motion influence sieving: vibratory motion is the most efficient, followed successively by side tap motion, bottom tap motion, and rotary motion with tap and rotary motion. Time is the important factor in sieving. The load or thickness of powder per unit area of sieve influences the time of sieving; for a given set of sieves, the time required to sieve a given material is roughly proportional to the load placed on the sieves, the type of motion, time of sieving, and load should be standardized.

Method:

Particle size distribution was determined by using sieve shaker. Approximately weighed amount i.e. 10g of a sample under study was kept at the top of the sieve, arranged in descending order of mesh size # i.e. 590μ, 420 μ, 250 μ, 149 μ, 74 μ and the base pan. The assembly was tightly closed and allowed to vibrate for 10 min at 10 HP. The amount of powder retained on each sieve was calculated.

Classification of powders depending on the particle size:

S.NO.	Type of Powder	Should Completely passing Through (Mesh no#)	NMT 60% should pass through (Mesh no#)
1	Coarse Powder	20	40
2	Moderately Coarse Powder	40	60
3	Fine Powder	80	120
4	Very Fine Powder	120	No limit

Table No.39

Angle of repose:

The flow property was determined by measuring the Angle of Repose. It is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane. Values of q are rarely less than 20°, and values of up to 40° indicate reasonable flow potential. Above 50o, however, the powder flows only with difficulty if at all.

$$\theta = \text{Tan}^{-1}(h/r)$$

Where,

h = height the pile.

r = radius of the pile.

θ = Angle of repose.

5 grams of the sample was taken in a funnel fixed in a holder, 6 cm above the surface at an appropriate height and a graph of sheet was placed below the funnel. The sample was passed through the funnel slowly. The height of the powder heap formed was measured. The circumference of the heap formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined using the above formula. This was repeated 3 times for a sample.

Determination of bulk density and tapped density:

A quantity of 20 g of the powder (W) from each formula was introduced into a 100 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to keep in bulk density apparatus for tapping. The tapping was continued until no further change in volume was noted.

The bulk density, and tapped density were calculated using the following

Formulas: -

Bulk density (ρ_0) = M/Vo

Where, M = mass of the powder

Vo = volume of the powder

Tapped density (ρ_t) = M/Vf

Where, M = weight of sample powder taken

Vf = tapped volume

Compressibility index (Carr's index):

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having value of less than 18 % is defined as the free flowing material.

$$CI = 100 (V0 - Vf) / V0$$

Where,

CI = Compressibility index.

Hausner's Ratio:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density / Bulk density.

LOSS ON DRYING:

In pharmacy, the term loss on drying, commonly referred to as LOD, is an expression of moisture content on a wet- weight basis, which is calculated as,

$$\% \text{ LOD} = \frac{\text{Weight of water in sample}}{\text{Weight of the sample}}$$

Method:

The moisture content of substances was determined gravimetrically on a SARTORIUS MA-45 moisture balance Approximately 1gm of sample was uniformly placed onto the sample pan and then the heating cycle was started. The percentage of moisture content was calculated from the weight loss of sample by heating. The instrument was allowed to cool between tests and triplicate test was run for each sample.

Tablet evaluation:[22]

The following tests are applied on uncoated tablet.

Appearance

The general appearance and elegance of tablet was identified visually, which include tablet size, shape, color, presence or absence of odour, taste, surface texture etc.

Description

Yellow, circular, flat, beveledged uncoated tablet having a breakline on oneside and other side plain.

Weight variation

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablets weight to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablets differ by more than two times the percent limit. The table given below shows the weight variation tolerance for uncoated tablets.

Weight variation tolerance for uncoated tablets:

Average Weight Of Tablets (mg)	Maximum Percentage Difference Allowed
80 or Less	10
80 – 250	7.5
More Than 250	5

Table No.40

Deviation was found was calculated as follows.

Maximum deviation:

$$+ Ve = (W_H - A) \times 100 / A$$

$$- Ve = (A - W_L) \times 100 / A$$

Where,

A = Average weight of tablets.

W_H = Highest weight of tablet in 20 tablets.

W_L = Lowest weight of tablet in 20 tablets.

Thickness:

The thickness of the tablets was measured using Digital Vernier Caliper. It is expressed in mm. Tablet thickness should be controlled within a ± 0.5 % variation of standard value.

Hardness:

Hardness is the crushing strength of tablets which determines the ease of handling and rigors of the transportation. The hardness of the tablets was measured using Erweka hardness tester. The instrument reads in kg / cm^2.

Friability:

Friability test is performed to assess the effect of friction and shocks, which may often cause tablets to chip or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches

with each revolution. Normally, a preweighed tablets sample is placed in friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that lose less than 0.5 to 1% of there weight are generally consider acceptable.

The percentage friability was measured using the formula:

$$\%F = \{(W-Wo) / Wo\} \times 100$$

Where %F = Friability in percentage

W = initial weight of tablets

Wo = weight of tablets after test

Disintegration time:

The USP device of test disintegration uses 6 glass tubes that are 3 inches long, open at the top, and held against a 10-mesh screen at the bottom end of the basket rack assembly. To test the disintegration time, one tablets is placed in each tube, and the basket rack was positioned in a 1-litre beaker of water, at 37°C±2°C, such that the tablets remains 2.5 cm below the surface of the liquid on there upward movement and descend not closer than 2.5 cm from the bottom of the beaker. A stander motor-driven device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minutes. This test was performed without using perforated plastic disc. To be in compliance with the USP standers, the tablets must disintegrate, and all particles must pass through the 10-mesh screen in the time specified. It is expressed in seconds. The time taken for each tablet to disintegrate was recorded.

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Drug content: (Assay)[34] (IN HOUSE METHOD)

This test determines the amount of active ingredient by the method in the assay.

Assay Method of Artemether for Formulation

Chromatographic Condition:

Column	:	C_{18}, 150 mm x 4.6 mm, 5 u (Inertsil ODS-3 C_{18} is suitable)
Detector	:	210 nm
Flow Rate	:	1.5 ml / min.
Injection Volume	:	50 µl
Column Temperature	:	Ambient.

Mobile Phase:

A mixture of Water (380 volumes) and Acetonitrile (620 volumes), mix properly, degas, and then filter through 0.45 um membrane filter Paper.

Diluent:

Mobile Phase

Standard Preparation:

Weight accurately 50 mg of Aretmether W.S. in 100 ml volumetric flask. Add 60 ml diluents, sonicate for 10 minutes and stir for 10 minuites, make up the volume with diluents.

Sample Preparation:

Weigh 20 tablets and crush to powder. Weigh accurately powder equivalent to 50 mg of Artermether in 100 ml volumetric flask. Add 60 ml diluents, sonicate for 15 minutes

and stir for 10 minutes and make up the volume with diluents. Filter the resulting solution through 0.45 um membrane filter Paper.

Procedure:

Separately inject 50 ul of the standard preparation in replicate and calculate RSD of standard area (RSD NMT 2.0%), Tailing factor (NMT 2.0), Theoretical plate NLT 1000 and inject test solution into the chromatogram and record the chromatograph and measure the response for the major peaks and calculate the result by comparison.

Calculation: Artemether (in %)

Spl area Std wt. 100 Std purity 100

= ----------X----------X----------X----------X----------X ---------- X

Average wt.

Avg.Std area 100 Spl wt 100 Label claim

Assay Method of Lumefantrine for Formulation (LUMEFANTRINE) :

Chromatographic Condition:

Column : C18, 150 mm x 4.6 mm, 5u (Phenomenex Gemini is suitable)

Detector : 380 mm

Flow Rate : 0.8 ml / min.

Column Temperature : Ambient

Buffer Preparation:

Take 1.5 gm of Ammonium acetate in 100o ml water; adjust pH 2.8 with dilute ortho phosphoric acid.

Mobile Phase:

A mixture of Buffer (300 volumes) and Acetonitrile (700 volumes), mix properly, degas, and then filter through 0.45 um membrane filter Paper.

Diluent:

Mobile phase

Standard preparation:

Weigh accurately 20 mg of Lumefantrine W.S. in 100 ml volumetric flack. Add 60 ml diluents, sonicate for 10 minutes and stir for 10 minutes, make up the volume with diluents. Dilute 5 ml of the resulting solution in 25 ml volumetric flask and make up volume with diluents.

Sample preparation:

Weigh 20 tablets and crush to powder. Weigh accurately powder equivalent to 20 mg of Lumefantrine in 100 ml volumetric flask. Add 60 mol diluents, sonicate for 30 minutes and stir for 10 minutes and make up the volume with diluents. Take 30 ml solution for centrifuge, Speed 2000 RPM for 10 min, and dilute 5 ml of the resulting solution in 25 ml volumetric flask and make up volume with diluents.

Procedure:

Separately inject 50 ul of the standard preparation in replicate and calculate RSD of standard area (RSD NMT 2.0%) and inject test solution into the chromatogram and

record the chromatograph and measure the response for the major peaks and calculate the result.

calculation:

Spl area Std wt. 5 100 25 Std purity 100

=----------X----------X----------X---------X----------X----------X----------X Average wt.

Avg.Std area 100 25 Spl wt 5 100 Label claim

In vitro dissolution study:[35]

Dissolution parameter for Artemether

Medium	:	900ml of Water
Apparatus	:	USP II (Paddle)
Speed	:	100 rpm
Time	:	180 minutes (30,60,90,120,180) min
Temperature	:	37º C ± 0.5 º C

Procedure :

Place the stated volume of dissolution medium in the vessels of the apparatus, assemble the apparatus and equilibrate the dissolution medium 37º C ± 0.5 º C, place one tablet in each of the vessels and immediate operate at specified rate after suspending the paddle. At the end of the specified time, withdraw the sample solution from the zone midway between the surface of the dissolution medium and top of the blade, not less than 1 cm from the vessel wall. Filter the sample solution through 0.8 um membrane filter; discard first few ml of the filtrate.

Standard Preparation:

Weigh accurately 40 mg of Artemether WS. In 100 ml volumetric flask, add 60 ml mobile phase sonicate to dissolve and make up the volume with mobile phase. Dilute 5 ml of the resulting solution in 100 ml volumetric flask and make up volume with dissolution media.

Chromatographic Condition, Mobile phase same as assay of Artermether:

Procedure:

Separately inject 100 µl of the standard preparation in replicate and calculate RSD of standard area (RSD NMT 2.0%) and inject assay preparation into the chromatogram and record the chromatograph and measure the response for the major peaks and calculate the result.

Calculation: Artemether (Release in %)

Spl abs Std wt. 5 1000 25 99 100

=----------X----------X----------X---------X----------X----------X----------X Average wt.

Std. abs 200 25 1 5 100 Label claim

Dissolution parameter for Lumefantrine

Medium	:	900ml of 0.1M Hydrochloric acid with 1% Benzal konium Chloride
Apparatus	:	USP II (Paddle)
Speed	:	100 rpm
Time	:	60 minutes (10,15,30,45,60) min
Temperature	:	37º C ± 0.5 º C

Procedure :

Place the stated volume of dissolution medium in the vessels of the apparatus, assemble the apparatus and equilibrate the dissolution medium to 37º C ± 0.5 º C, place one tablet in each of the vessels and immediate operate at specified rate after suspending the paddle. At the end of the specified time, withdraw the sample solution from the zone midway between the surface of the dissolution medium and top of the blade, not less than 1 cm from the vessel wall. Filter the sample solution through 0.8 µm membrane filter, discard first few ml of the filtrate. Dilute 5 ml of the resulting solution in 25 ml volumetric flask and make up volume with mobile phase.

Standard Preparation:

Weigh accurately 22 mg of Lumefantrine WS. in 200 ml volumetric with Acetonitrile. Dilute 5 ml of the resulting solution in 25 ml volumetric flask and make up volume with dissolution media.

Chromatographic Condition, Mobile phase same as assay of Lumfantrine:

Procedure:

Separately inject 100 ml of the standard preparation in replicate and calculate RSD of standard area (RSD NMT 2.0 %) and inject assay preparation into the chromatogram and record he chromatograph and measure the response for the major peaks and calculate the result.

Calculation: Lumefantrine (Release in %)

Spl abs Std wt. 5 1000 99.2 100

=----------X----------X----------X---------X----------X----------X Average wt.

Std. abs 100 100 1 100 Label claim

Similarity Factor and Difference Factor Calculation (In house method)

The similarity factor (f2) was defined by CDER, FDA, and EMEA as the ―logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and refrence release profiles.

Dissimilarity or difference factor (f1) describes the relative error between two dissolution profiles. It approximates the percent error between the curves. The percent error is zero when the test and reference release profiles are identical and increases proportionally with the dissimilarity between the two profiles.There are several methods for dissolution profile comparison. f2 is the simplest among those methods. Moore & Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors f1 & f2.

$$f1 = \{ [\sum_{t=1}^{n} Rt - Tt] / [\sum_{t=1}^{n} Rt] \} . 100 \qquad \text{eq (1)}$$

$$f2 = 50. \text{Log} \{ [1 + (1/n) \sum_{t=1}^{n} (Rt - Tt)^2] - 0.5 . 100 \} \qquad \text{eq (2)}$$

where 'Rt' and 'Tt' are the cumulative percentage dissolved at each of the selected n time point of the reference & test product respectively. The factor *f1* is proportional to the average difference between the two profiles, where as factor *f2* is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points. The similarity factor *f2* and its significance is shown in the following.

Similarity factor *f2* and its significance

1.	<50	Test and reference profiles are dissimilar.
2.	50 -100	Test and reference profiles are similar.
3.	100	Test and reference profiles are identical.
4.	>100	The equation yields a negative value.

Table No.41

Similarity factor (f_2)and dissimilar factors (f_1)**.** The test and reference release profiles of artemether and lumefantrine Were performed and results was found.

Observation for different trial batches:

Physical characterization of blends of all Trial batches.

Trial	**Bulk Density (g / cc)**	**Tapped Density (g / cc)**	**%Compressibility index**	**Hausner's ratio**
F1	0.5089	0.6694	23.98	1.32
F2	0.5069	0.7060	28.21	1.39
F3	0.5133	0.6673	23.08	1.30
F4	0.5091	0.7202	29.33	1.41

Table No.42

Particle size distribution of all Trial batches:

Sieve No.	**Percentage Retained**			
	F1	F2	F3	F4
30#	7.69	9.32	7.048	9.73
40#	38.69	43.76	39.013	43.65
60#	19.04	20.61	19.53	20.98
100#	10.36	12.89	10.06	11.98
Base pan	24.22	13.42	29.44	13.66

Table No.43

Total amount of blend = 25 g.

Physical characterization of uncoated Artemther and Lumefantrine trial batches:

Trial	Average weight (g)	Thickness (mm)	Diameter (mm)	Hardness (Kg / cm^2)	Friability (% W/W)	DT
F1	2.405	3.1	9.0	5	0.21	45 sec
F2	2.400	3.2	9.0	4.5	0.11	2 min 20 sec
F3	2.423	3.0	9.1	5	0.07	2 min 40 sec
F4	2.388	3.1	9.1	5	0.16	3 min 18 sec

Table No.44

Uniformity of Weight Test for Tablets – Trial F3

Sl.No.	Weight of tablet (mg)	Deviation	% Deviation
1	0.2448	0.0025	1.0318
2	0.2433	0.0010	0.4127
3	0.2435	0.0012	0.4953
4	0.2418	-0.0005	-0.2064
5	0.2439	0.0016	0.6603
6	0.2434	0.0011	0.4540
7	0.2394	-0.0029	-1.1969
8	0.2421	-0.0002	-0.0825
9	0.2418	-0.0005	-0.2064
10	0.2398	-0.0025	-1.0318
11	0.2427	0.0004	0.1651
12	0.2427	0.0004	0.1651
13	0.2433	0.0010	0.4127
14	0.2429	0.0006	0.2476

15	0.2425	0.0002	0.0825
16	0.2404	-0.0019	-0.7842
17	0.2416	-0.0007	-0.2889
18	0.2439	0.0016	0.6603
19	0.2421	-0.0002	-0.0825
20	0.2401	-0.0022	-0.9080

Table No.45

Wt. Of 20 tabs	4.8457g
Average Wt. Of 1 tab	0.2423g

All the tablets were passed the Uniformity of Weight test. The tablets had average weights ranging from 0.24 to 0.36g

Dissolution profile – F1(A)

MEDOPHARM PRIVATE LIMITED, GUDUVANCHERY

R&D ANALYTICAL DEPARTMENT

DIFFERENCE FACTOR (F1) & SIMILARITY FACTOR (F2)

Product name	F 1	Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.	F 1	Manufactrer	Medopharm PVT. LTD
Mfg.date		A.R. No.	ARD-2368
Exp.date		Date of Analysis	
Innovator / Reference	Coartem	Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.	F2772	Manufactrer	Novartis
Mfg.date	Feb-12	Date of Analysis	
Exp.date	Jan-14		

Dissolution parameter :

BY HPLC

ARTEMETHER

Medium : 1000ml of water.
Apparatus : USP II (Paddle)
Speed : 100 RPM
Time interval : 30min., 60min., 90min.,120min. & 180min.

Time point	Coartem	F1	Rt-Tt	$(Rt-Tt)^2$	|Rt-Tt|
0	0.00	0.00	0.00	0.00	0.00
30	45.67	38.42	3.64	52.56	7.25
60	62.30	56.89	4.20	29.27	5.41
90	72.93	68.25	1.22	21.90	4.68
120	80.18	74.86	-2.60	28.30	5.32
180	89.16	81.92	-7.15	52.42	7.24
SUM	350.24			184.45	29.90
Number of Time points or intervals[Excluding zero]					5
Difference Factor - F1[Acceptance Criteria : 0 - 15]					8.54
Similarity Factor - F2[Acceptance Criteria : 50 - 100]					60.54

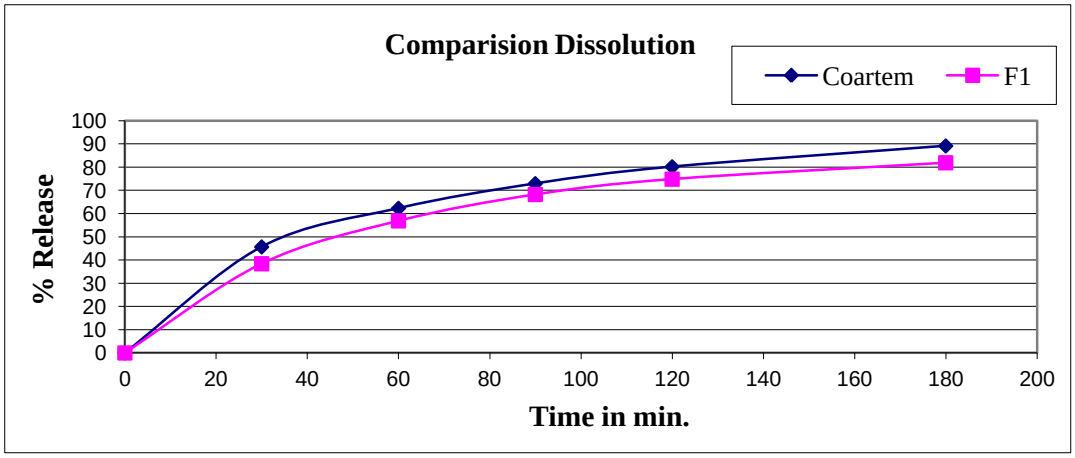
Table – 46

Dissolution profile – F1(L)

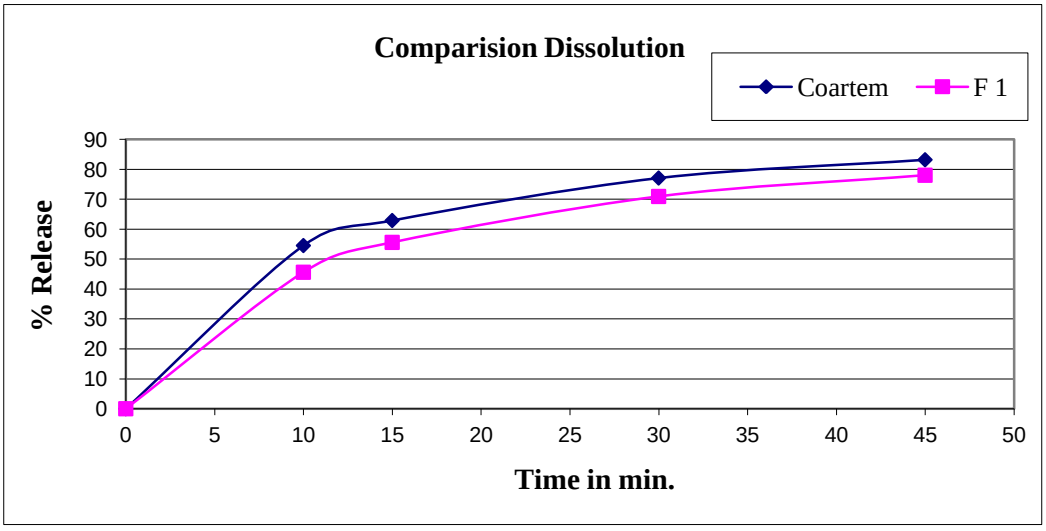
	MEDOPHARM PRIVATE LIMITED, GUDUVANCHERY				
	R&D ANALYTICAL DEPARTMENT				
	DIFFERENCE FACTOR (F1) & SIMILARITY FACTOR (F2)				
Product name		F 1		Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.		F 1		Manufactrer	Medopharm PVT. LTD
Mfg.date				A.R. No.	ARD-2363
Exp.date				Date of Report	
Innovator / Reference		Coartem		Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.		F2772		Manufactrer	Novartis
Mfg.date		Feb-12		Date of Report	
Exp.date		Jan-14			
Dissolution parameter : Medium : 1000ml of 0.1 M HCl with 1% BKC. Apparatus : USP II (Paddle) Speed : 75 RPM Time interval : 10min., 15min., 30min., 45min. & 60min.					
BY UV					
LUMEFANTRINE					
Time point	Coartem	F 1	Rt-Tt	$(Rt-Tt)^2$	|Rt-Tt|
0	0.00	0.00	0.00	0.00	0.00
10	54.50	45.59	8.91	79.39	8.91
15	62.87	55.56	7.31	53.44	7.31
30	77.05	70.90	6.15	37.82	6.15
45	83.15	77.99	5.16	26.63	5.16
60	85.89	83.11	2.78	7.73	2.78
SUM	363.46			205.00	30.31
Number of Time points or intervals[Excluding zero]					5
Difference Factor - F1[Acceptance Criteria : 0 - 15]					8.34
Similarity Factor - F2[Acceptance Criteria : 50 - 100]					59.42

Table no-47

Dissolution profile – F1(A&L) (Graphical report)



CONCLUSION : The difference factor (F1) & Similarity factor (F2)
not Similar when compared with reference product



CONCLUSION : The difference factor (F1) & Similarity factor (F2)
not similar when compared with reference product

Fig no- 11

Dissolution profile – F2(A)

MEDOPHARM PRIVATE LIMITED, GUDUVANCHERY R&D ANALYTICAL DEPARTMENT DIFFERENCE FACTOR (F1) & SIMILARITY FACTOR (F2)					
Product name		F 2		Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.		F 2		Manufactrer	Medopharm PVT. LTD
Mfg.date				A.R. No.	ARD-2368
Exp.date				Date of Analysis	
Innovator / Reference		Coartem		Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.		F2772		Manufactrer	Novartis
Mfg.date		Feb-12		Date of Analysis	
Exp.date		Jan-14			
Dissolution parameter : BY HPLC ARTEMETHER		Medium : 1000ml of water. Apparatus : USP II (Paddle) Speed : 100 RPM Time interval : 30min., 60min., 90min.,120min. & 180min.			
Time point	Coartem	F 2	Rt-Tt	$(Rt-Tt)^2$	|Rt-Tt|
0	0.00	0.00	0.00	0.00	0.00
30	45.67	48.68	4.01	9.06	3.01
60	62.30	68.30	-2.88	36.00	6.00
90	72.93	77.72	-7.17	22.94	4.79
120	80.18	83.06	0.07	8.29	2.88
180	89.16	89.08	0.08	0.01	0.08
SUM	350.24			76.30	16.76
Number of Time points or intervals[Excluding zero]					5
Difference Factor - F1[Acceptance Criteria : 0 - 15]					4.79
Similarity Factor - F2[Acceptance Criteria : 50 - 100]					69.72

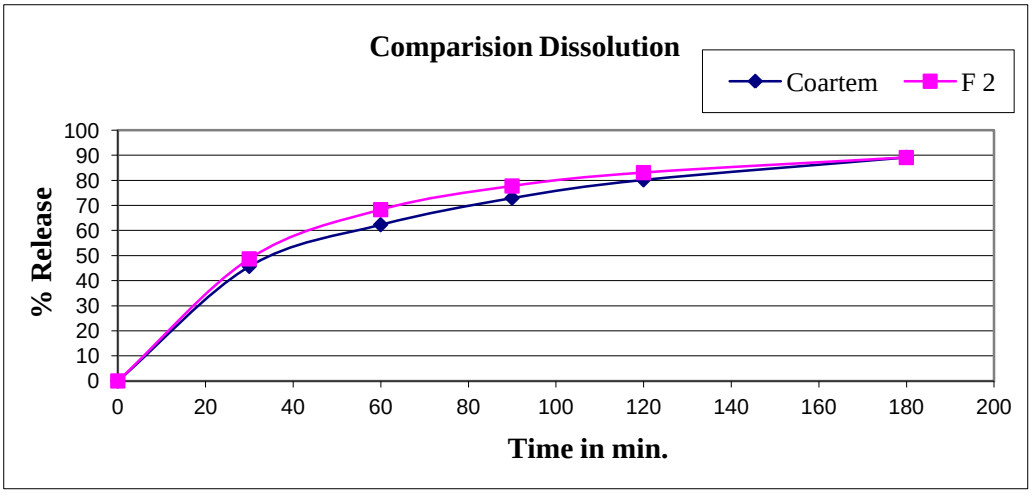
Table no – 48

Dissolution profile – F2(L)

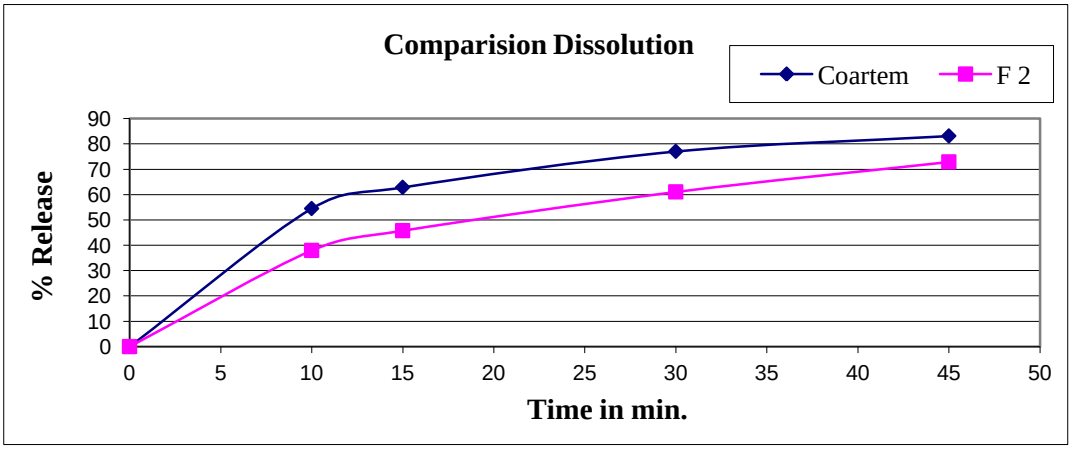
MEDOPHARM PRIVATE LIMITED, GUDUVANCHERY					
R&D ANALYTICAL DEPARTMENT					
DIFFERENCE FACTOR (F1) & SIMILARITY FACTOR (F2)					
Product name		F 2		Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.		F 2		Manufactrer	Medopharm PVT. LTD
Mfg.date				A.R. No.	ARD-2314
Exp.date				Date of Report	
Innovator / Reference		Coartem		Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.		F2772		Manufactrer	Novartis
Mfg.date		Feb-12		Date of Report	
Exp.date		Jan-14			
Dissolution parameter : Medium : 1000ml of 0.1 M HCl with 1% BKC. Apparatus : USP II (Paddle) Speed : 75 RPM Time interval : 10min., 15min., 30min., 45min. & 60min.					
BY UV					
LUMEFANTRINE					
Time point	Coartem	F 2	Rt-Tt	$(Rt-Tt)^2$	$\lvert Rt-Tt \rvert$
0	0.00	0.00	0.00	0.00	0.00
10	54.50	37.95	16.55	273.90	16.55
15	62.87	45.77	17.10	292.41	17.10
30	77.05	61.06	15.99	255.68	15.99
45	83.15	72.89	10.26	105.27	10.26
60	85.89	79.10	6.79	46.10	6.79
SUM	363.46			973.36	66.69
Number of Time points or intervals[Excluding zero]					5
Difference Factor - F1[Acceptance Criteria : 0 - 15]					18.35
Similarity Factor - F2[Acceptance Criteria : 50 - 100]					42.71

Table no- 49

Dissolution profile – F2 (A&L)(Graphical report)



CONCLUSION : The difference factor (F1) & Similarity factor (F2) not similar when compared with reference product



CONCLUSION : The difference factor (F1) & Similarity factor (F2) not similar when compared with reference product

Fig no-12

Dissolution profile – F3(A)

	MEDOPHARM PRIVATE LIMITED, GUDUVANCHERY				
	R&D ANALYTICAL DEPARTMENT				
DIFFERENCE FACTOR (F1) & SIMILARITY FACTOR (F2)					
Product name		F 3		Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.		F-3		Manufactrer	Medopharm PVT. LTD
Mfg.date		Dec-12		A.R. No.	ARD-2314
Exp.date		Nov-14		Date of Analysis	
Innovator / Reference		Coartem		Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.		F2772		Manufactrer	Novartis
Mfg.date		Feb-12		Date of Analysis	
Exp.date		Jan-14			
Dissolution parameter : BY HPLC ARTEMETHER		Medium : 1000ml of water. Apparatus : USP II (Paddle) Speed : 100 RPM Time interval : 30min., 60min., 90min.,120min. & 180min.			

Time point	Coartem	F 3	Rt-Tt	$(Rt-Tt)^2$	|Rt-Tt|
0	0.00	0.00	0.00	0.00	0.00
30	40.52	36.46	4.06	16.48	4.06
60	56.10	63.27	-7.17	51.41	7.17
90	66.24	78.04	-11.80	139.24	11.80
120	74.35	85.85	-11.50	132.25	11.50
180	81.53	93.85	-12.32	151.78	12.32
SUM	318.74			491.16	46.85

Number of Time points or intervals[Excluding zero]	5
Difference Factor - F1[Acceptance Criteria : 0 - 15	14.70
Similarity Factor - F2[Acceptance Criteria : 50 - 100]	50.08

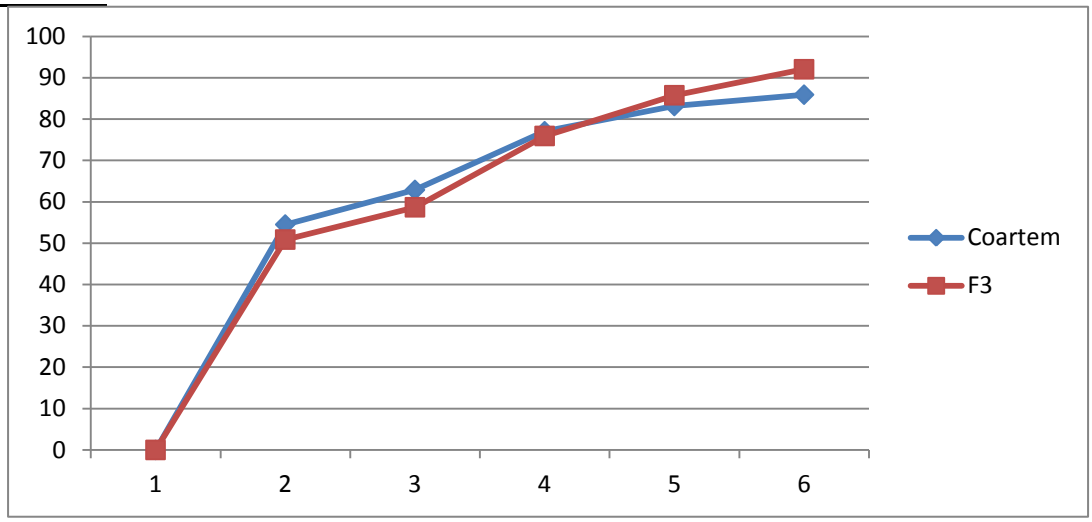
Table no-50

Dissolution profile – F3(L)

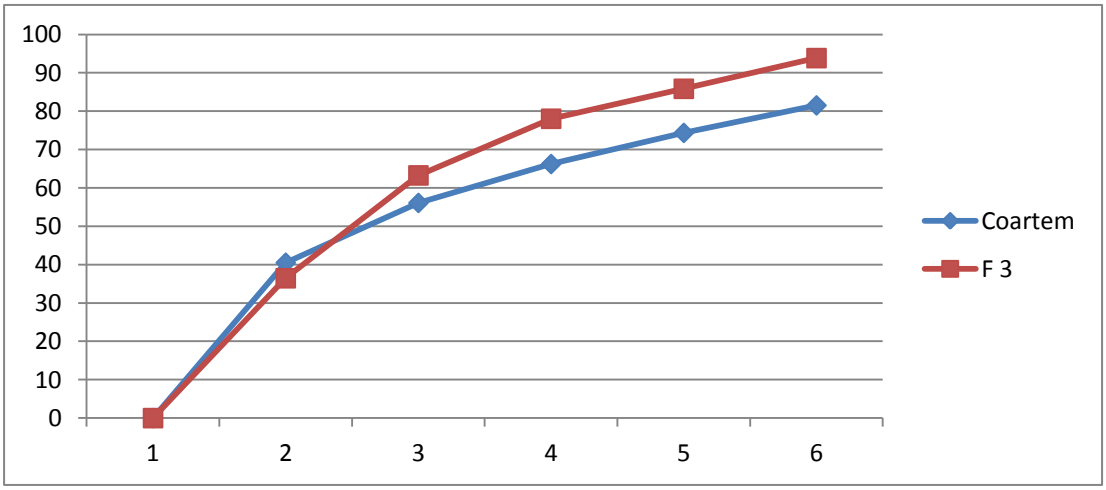
MEDOPHARM PRIVATE LIMITED, GUDUVANCHERY R&D ANALYTICAL DEPARTMENT DIFFERENCE FACTOR (F1) & SIMILARITY FACTOR (F2)					
Product name		F 3	Artemether & Lumefantrine Tablets 20+120mg		
Batch no. /Lot no.		F3	Manufactrer		
Mfg.date		Dec-12	A.R. No.	ARD-2272	
Exp.date			Date of Analysis		
Innovator / Reference		Coartem	Artemether & Lumefantrine Tablets 20+120mg		
Batch no. /Lot no.		F2772	Manufactrer	Novartis	
Mfg.date		Feb-12	Date of Analysis		
Exp.date		Jan-14			
Dissolution parameter : BY UV LUMEFANTRINE		Medium : 1000ml of 0.1 M HCl with 1% BKC. Apparatus : USP II (Paddle) Speed : 75 RPM Time interval : 10min., 15min., 30min., 45min. & 60min.			
Time point	Coartem	F3	Rt-Tt	$(Rt-Tt)^2$	|Rt-Tt|
0	0.00	0.00	0.00	0.00	0.00
10	54.50	50.86	3.64	13.25	3.64
15	62.87	58.67	4.20	17.64	4.20
30	77.05	75.91	1.14	1.30	1.14
45	83.15	85.76	-2.61	6.81	2.61
60	85.89	92.04	-6.15	37.82	6.15
SUM	363.46			76.82	17.74
Number of Time points or intervals[Excluding zero]					5
Difference Factor - F1[Acceptance Criteria : 0 - 15]					4.88
Similarity Factor - F2[Acceptance Criteria : 50 - 100]					69.65

Table no -51

Dissolution profile – F3 (A&L)(Graphical report)



CONCLUSION : The difference factor (F1) & Similarity factor (F2) similar when compared with reference product



CONCLUSION : The difference factor (F1) & Similarity factor (F2) similar when compared with reference product

Fig no – 13

Dissolution profile – F4(A)

	MEDOPHARM PRIVATE LIMITED, GUDUVANCHERY **R&D ANALYTICAL DEPARTMENT**				
	DIFFERENCE FACTOR (F1) & SIMILARITY FACTOR (F2)				
Product name		F 4		Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.		F 4		Manufactrer	Medopharm PVT. LTD
Mfg.date				A.R. No.	ARD2367
Exp.date				Date of Report	
Innovator / Reference		Coartem		Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.		F2772		Manufactrer	Novartis
Mfg.date		Feb-12		Date of Report	
Exp.date		Jan-14			
Dissolution parameter : BY HPLC ARTEMETHER		Medium : 1000ml of water. Apparatus : USP II (Paddle) Speed : 100 RPM Time interval : 30min., 60min., 90min.,120min. & 180min.			
Time point	Coartem	F 4	Rt-Tt	$(Rt-Tt)^2$	|Rt-Tt|
0	0.00	0.00	0.00	0.00	0.00
30	38.49	37.16	1.33	1.77	1.33
60	54.61	53.16	1.45	2.10	1.45
90	63.19	58.44	4.75	22.56	4.75
120	70.17	67.28	2.89	8.35	2.89
180	79.58	74.66	4.92	24.21	4.92
SUM	306.04			58.99	15.34
Number of Time points or intervals[Excluding zero]					5
Difference Factor - F1[Acceptance Criteria : 0 - 15]					5.01
Similarity Factor - F2[Acceptance Criteria : 50 - 100]					72.32

Table no – 52

Dissolution profile – F4(L)

MEDOPHARM PRIVATE LIMITED, GUDUVANCHERY

R&D ANALYTICAL DEPARTMENT

DIFFERENCE FACTOR (F1) & SIMILARITY FACTOR (F2)

Product name	F 4	Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.	F 4	Manufactrer	Medopharm PVT. LTD
Mfg.date		A.R. No.	ARD-2314
Exp.date		Date of Report	
Innovator / Reference	Coartem	Artemether & Lumefantrine Tablets 20+120mg	
Batch no. /Lot no.	F2772	Manufactrer	Novartis
Mfg.date	Feb-12	Date of Report	
Exp.date	Jan-14		

Dissolution parameter :

BY UV

LUMEFANTRINE

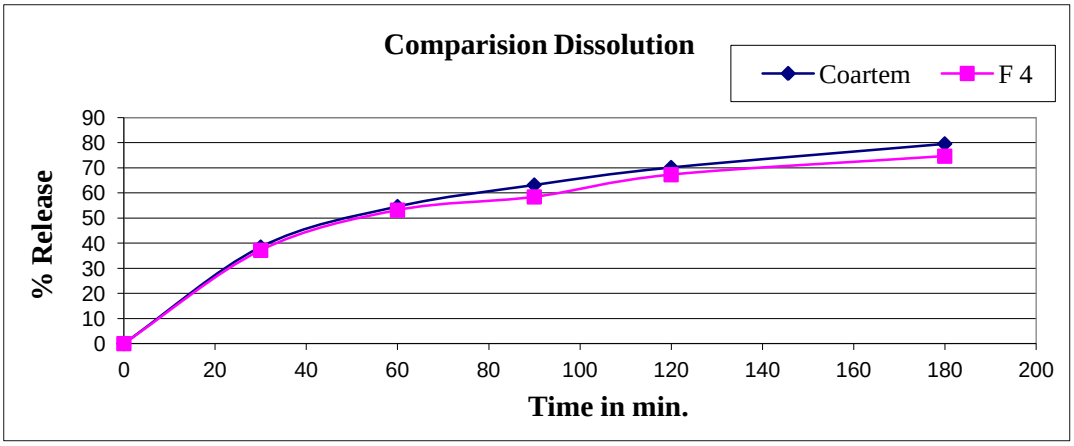
Medium : 1000ml of 0.1 M HCl with 1% BKC.
Apparatus : USP II (Paddle)
Speed : 75 RPM
Time interval : 10min., 15min., 30min., 45min. & 60min.

Time point	Coartem	F 4	Rt-Tt	$(Rt-Tt)^2$	|Rt-Tt|
0	0.00	0.00	0.00	0.00	0.00
10	54.50	38.54	15.96	254.72	15.96
15	62.87	46.54	16.33	266.67	16.33
30	77.05	62.38	14.67	215.21	14.67
45	83.15	73.74	9.41	88.55	9.41
60	85.89	80.72	5.17	26.73	5.17
SUM	363.46			851.88	61.54

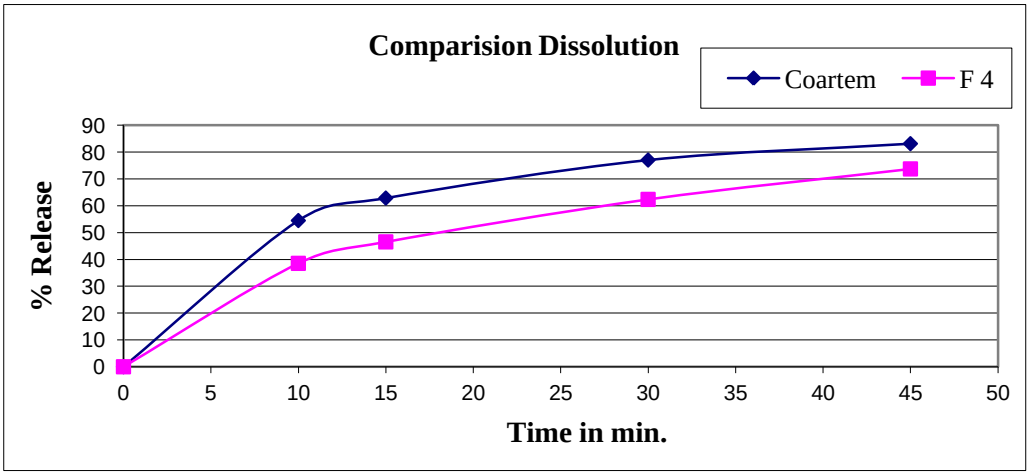
Number of Time points or intervals[Excluding zero]	5
Difference Factor - F1[Acceptance Criteria : 0 - 15]	16.93
Similarity Factor - F2[Acceptance Criteria : 50 - 100]	44.15

Table no -53

Dissolution profile – F4 (A&L)(Graphical report)



CONCLUSION : The difference factor (F1) & Similarity factor (F2)
not similar when compared with reference product



CONCLUSION : The difference factor (F1) & Similarity factor (F2)
Not similar when compared with reference product

Fig no – 14

Assay parameter-F1(A)

MEDOPHARM PRIVATE LIMITED,GUDUVANCHERY

R&D Analytical Department

Product Name:Artemether(20)+Lumefantrine(120mg) Tablets.

Batch No.: F1

Assay : Content of Artemether **project data**

Standard Preparation: 51.1mg -----> 100ml@ Mobile phase

Test Preparation : 828.2mg tabs powder. ---------> 100ml@Mobile phase

Name of Std	**% of purity**	
Artemether	99.22	Average wt of tablet 330.9mg

	Artemether std area	**Artemether spl area**	**Assay in mg**	**Assay in %**
	706730	669650		
	684719	671836		
	683506			
	682443		19.75	98.7
	683080			
Average	**688096**	**670743**		
Stdev	10450			
RSD	1.52			

Table no- 54

Assay parameter-F1(L)

MEDOPHARM PRIVATE LIMITED,GUDUVANCHERY				
R&D Analytical Department				
Product Name: Artemether + Lumefantrine (20+120)mg Tablets **Batch No.: F1** **Assay :**Content of Lumefantrine **Standard Preparation: 20.0**mg -----> 100ml, 5ml-------->25ml@ Mobile phase **Test Preparation :** 48.2mg tabs powder. ---------> 100ml,5------->25ml @Mobile phase.				
Name of Std	**% of purity**	Average wt. of Tablet: 241.7mg		
Lumefantrine	99.0			
	Std area	**Spl area**	**Assay in mg**	**Assay in %**
	1115146	1323473		
	1112896	1323730		
	1113794			
	1114558		118.16	98.5
	1116275			
Average	**1114534**	**1323602**		
Stdev	1288			
RSD	0.12			

Table no-55

Assay parameter-F1(A)

MEDOPHARM PRIVATE LIMITED,GUDUVANCHERY

R&D Analytical Department

Product Name:Artemether(20)+Lumefantrine(120mg) Tablets.

Batch No.: F2

Assay : Content of Artemether

Standard Preparation: 51.1mg -----> 100ml@ Mobile phase

Test Preparation : 915.2mg tabs powder. ---------> 100ml@Mobile phase

Name of Std	% of purity	
Artemether	99.22	Average wt of tablet 330.9mg

	Artemether std area	Artemether spl area	Assay in mg	Assay in %
	706730	741646		
	684719	742166		
	683506			
	682443		19.77	98.8
	683080			
Average	**688096**	**741906**		
Stdev	10450			
RSD	1.52			

Table no -56

Assay parameter-F2(L)

MEDOPHARM PRIVATE LIMITED,GUDUVANCHERY

R&D Analytical Department

Product Name: Artemether + Lumefantrine (20+120)mg Tablets

Batch No.: F2

Assay : Content of
Lumefantrine

Standard Preparation: 20.1mg -----> 100ml, 5ml------->25ml@ Mobile phase

Test Preparation : 44.5mg tabs powder. ---------> 100ml,5------->25ml @Mobile phase.

Name of Std	**% of purity**	Average wt. of Tablet: 240.4mg
Lumefantrine	99.0	

	Std area	**Spl area**	**Assay in mg**	**Assay in %**
	1044466	1140725		
	1040008	1138185		
	1039717			
	1046149		117.55	98.0
	1039795			
Average	**1042027**	**1139455**		
Stdev	3055			
RSD	0.29			

Table no-57

Assay parameter-F3(A)

MEDOPHARM PRIVATE LIMITED,GUDUVANCHERY

R&D Analytical Department

Product Name:Artemether(20)+Lumefantrine(120mg) Tablets.

Batch No.:F-3

Assay : Content of Artemether

Standard Preparation: 50.7mg -----> 100ml@ Mobile phase

Test Preparation : 604.6mg tabs powder. ---------> 100ml@Mobile phase

Name of Std	% of purity		
Artemether	99.22	Average wt of tablet	241.7mg

Artemether std area		Artemether spl area	Assay in mg	Assay in %
	Apr-13	Mar-90		
	Jan-13	Oct-83		
	Feb-12			
	Nov-11		19.84	99.2
	Sep-17			
Average	**735457**	**725735**		
Stdev	859			
RSD	0.12			

Table no-58

Assay parameter-F3 (L)

MEDOPHARM PRIVATE LIMITED,GUDUVANCHERY

R&D Analytical Department

Product Name:Artemether(20)+ Lumefantrine(120) tablets

Batch No.: F-3

Assay : Content of Lumefantrine

Standard Preparation: 20.2mg -----> 100ml, 5ml------->25ml@ Mobile phase
Test Preparation : 55.0mg tabs powder. ----------> 100ml,5------->25ml @Mobile phase.

Name of Std	**% of purity**	Average wt. of Tablet: 333.9mg
Lumefantrine	99.0	

	Std area	**Spl area**	**Assay in mg**	**Assay in %**
	Nov-71	Jan-19		
	Oct-69	May-24		
	Jun-73			
			119.43	99.5
Average	**1121925**	**1103650**		
Stdev	681			
RSD	0.06			

Table no-59

Assay parameter-F4 (A)

MEDOPHARM PRIVATE LIMITED,GUDUVANCHERY				
R&D Analytical Department				
Product Name:Artemether(20)+Lumefantrine(120mg) Tablets. **Batch No.: F 4** **Assay :**Content of Artemether **Standard Preparation:** 50.5mg -----> 100ml@ Mobile phase **Test Preparation :** 685.3mg tabs powder. ---------> 100ml@Mobile phase				
Name of Std		**% of purity**		
Artemether		99.22	Average wt of tablet 240.1mg	
Artemether std area		**Artemether spl area**	**Assay in mg**	**Assay in %**
	2E+06	1479891		
	2E+06	1476767		
	2E+06			
	2E+06		19.68	98.4
	2E+06			
	2E+06			
Average	######	**1478329**		
Stdev	614			
RSD	0.04			

Table no-60

Assay parameter-F4 (L)

MEDOPHARM PRIVATE LIMITED,GUDUVANCHERY

R&D Analytical Department

Product Name: Artemether + Lumefantrine (20+120)mg Tablets

Batch No.: F4

Assay : Content of
Lumefantrine

Standard Preparation: 20.0mg -----> 100ml, 5ml------->25ml@ Mobile phase

Test Preparation : 40.2mg tabs powder. ---------> 100ml,5------->25ml @Mobile phase.

Name of Std	**% of purity**	Average wt. of Tablet: 241.7mg	
Lumefantrine	99.0		

Std area	**Spl area**	**Assay in mg**	**Assay in %**
1E+06	1095095		
1E+06	1096615		
1E+06			
1E+06		117.05	97.5
1E+06			

Average	######	**1095855**
Stdev	1288	
RSD	0.12	

Table no – 61

Assay parameter-COARTEM (A)

MEDOPHARM PRIVATE LIMITED,GUDUVANCHERY

R&D Analytical Department

Product Name:Coartem Tablets (20+120)mg

Batch No.: F2772

Assay : Content of Artemether

Standard Preparation: 50.4mg -----> 100ml@ Mobile phase

Test Preparation : 605.7mg tabs powder. ---------> 100ml@Mobile phase

Name of Std	% of purity	
Artemether	99.22	Average wt of tablet 241.9mg

	Artemether std area	Artemether spl area	Assay in mg	Assay in %
	720847	689486		
	719376	690339		
	720388			
	718979		19.15	95.7
	720025			
	718091			
Average	**719618**	**689913**		
Stdev	1007			
RSD	0.14			

Table no – 62

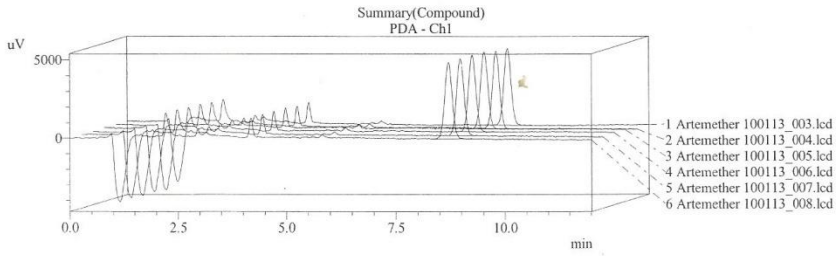
Assay parameter-COARTEM (L)

MEDOPHARM PRIVATE LIMITED,GUDUVANCHERY			
R&D Analytical Department			
Product Name: Coartem 20/120 Tablets (Novartis). **Batch No.: F2772** **Assay :**Content of Lumefantrine **Standard Preparation: 20.5**mg -----> 100ml, 5ml-------->25ml@ Mobile phase **Test Preparation :** 43.1mg tabs powder. ---------> 100ml,5-------->25ml @Mobile phase.			
Name of Std	**% of purity**	Average wt. of Tablet: 238.4mg	
Lumefantrine	99.0		
Std area	**Spl area**	**Assay in mg**	**Assay in %**
1082861	1101175		
1084065	1098222		
1083031			
1082984		114.02	95.0
1081957			
1081596			
Average	**1082749**	**1099699**	
Stdev	876		
RSD	0.08		

Table no - 63

MEDOPHARM PRIVATE LIMITED
R&D Analytical Department
SHEMADZU LC-Solution Analysis report

SUMMARY REPORT



<< PDA >>
ID#1 Compound Name: Artemether

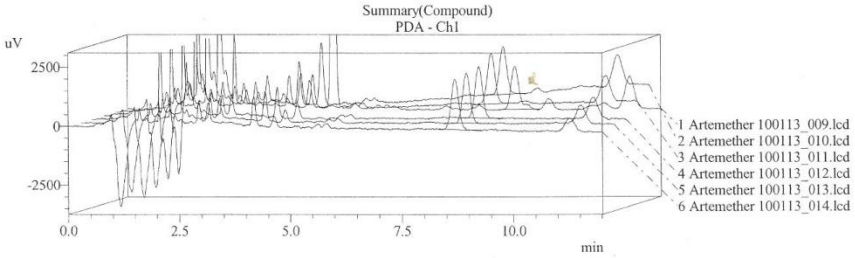
Sample Name	Sample ID	Ret. Time	Area	eoretical Pla	Tailing Factor
Artemether	Dissolution Std	8.722	58939	11514	1.058
Artemether	Dissolution Std	8.719	57709	11600	1.034
Artemether	Dissolution Std	8.715	58378	11379	1.046
Artemether	Dissolution Std	8.708	57846	11422	1.041
Artemether	Dissolution Std	8.709	58057	11412	1.039
Artemether	Dissolution Std	8.706	59086	11238	1.044
		8.713	58336	11428	1.044
		0.078	0.981	1.077	0.768

Analysed By:

Checked By:

MEDOPHARM PRIVATE LIMITED
R&D Analytical Department
SHEMADZU LC-Solution Analysis report

SUMMARY REPORT



<< PDA >>
ID#1 Compound Name: Artemether

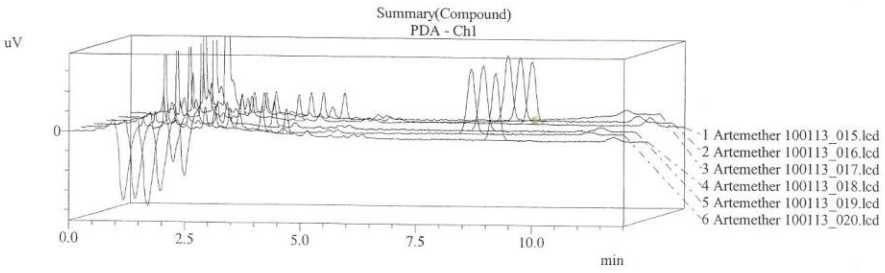
Sample Name	Sample ID	Ret. Time	Area	eoretical Pla	Tailing Factor
Artemether+Lumefantrine Tablet (20+120)mg	No.13ALT12401 Disso(30M	8.706	23826	10579	1.477
Artemether+Lumefantrine Tablet (20+120)mg	No.13ALT12401 Disso(30M	8.703	23599	11807	1.029
Artemether+Lumefantrine Tablet (20+120)mg	No.13ALT12401 Disso(30M	8.706	25569	11146	1.006
Artemether+Lumefantrine Tablet (20+120)mg	No.13ALT12401 Disso(30M	8.684	25440	11254	1.045
Artemether+Lumefantrine Tablet (20+120)mg	No.13ALT12401 Disso(30M	8.672	24451	11668	1.070
Artemether+Lumefantrine Tablet (20+120)mg	No.13ALT12401 Disso(30M	8.683	25446	11290	1.072
		8.692	24722	11291	1.117
		0.169	3.570	3.835	15.987

Analysed By:

Checked By:

MEDOPHARM PRIVATE LIMITED
R&D Analytical Department
SHEMADZU LC-Solution Analysis report

SUMMARY REPORT



<< PDA >>
ID#1 Compound Name: Artemether

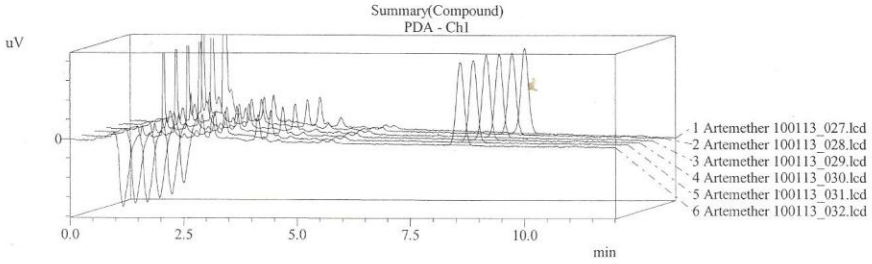
Sample Name	Sample ID	Ret. Time	Area	coretical Pla	Tailing Factor
Artemether+Lumefantrine Tablet (20+120)mg	No.13ALT12401 Disso(60M	8.677	37234	11143	1.005
Artemether+Lumefantrine Tablet (20+120)mg	No.13ALT12401 Disso(60M	8.673	37913	11042	1.045
Artemether+Lumefantrine Tablet (20+120)mg	No.13ALT12401 Disso(60M	8.674	39974	11158	1.088
Artemether+Lumefantrine Tablet (20+120)mg	No.13ALT12401 Disso(60M	8.669	40148	11208	1.043
Artemether+Lumefantrine Tablet (20+120)mg	No.13ALT12401 Disso(60M	8.671	39286	11175	1.029
Artemether+Lumefantrine Tablet (20+120)mg	No.13ALT12401 Disso(60M	8.683	39855	10808	1.015
		8.674	39068	11089	1.038
		0.060	3.103	1.339	2.820

Analysed By:

Checked By:

MEDOPHARM PRIVATE LIMITED
R&D Analytical Department
SHEMADZU LC-Solution Analysis report

SUMMARY REPORT



<< PDA >>
ID#1 Compound Name: Artemether

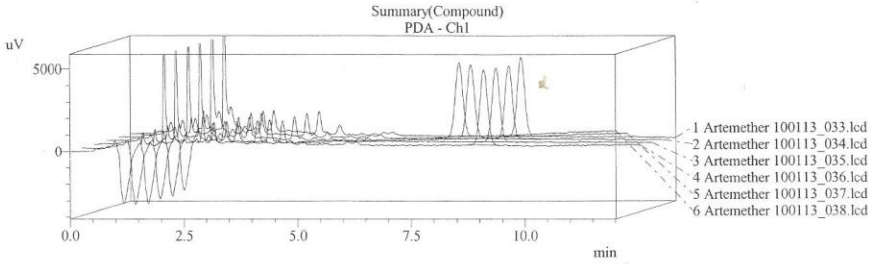
Sample Name	Sample ID	Ret. Time	Area	eoretical Pla	Tailing Factor
Artemether+Lumefantrine Tablet (20+120)mg	lo.13ALT12401 Disso(120M	8.672	52540	11168	1.019
Artemether+Lumefantrine Tablet (20+120)mg	lo.13ALT12401 Disso(120M	8.650	49185	11270	1.044
Artemether+Lumefantrine Tablet (20+120)mg	lo.13ALT12401 Disso(120M	8.635	50404	11290	1.048
Artemether+Lumefantrine Tablet (20+120)mg	lo.13ALT12401 Disso(120M	8.619	52160	11105	1.019
Artemether+Lumefantrine Tablet (20+120)mg	lo.13ALT12401 Disso(120M	8.608	49402	11395	1.018
Artemether+Lumefantrine Tablet (20+120)mg	lo.13ALT12401 Disso(120M	8.587	49687	11078	1.027
		8.628	50563	11218	1.029
		0.352	2.866	1.086	1.301

Analysed By:

Checked By:

MEDOPHARM PRIVATE LIMITED
R&D Analytical Department
SHEMADZU LC-Solution Analysis report

SUMMARY REPORT



<< PDA >>
ID#1 Compound Name: Artemether

Sample Name	Sample ID	Ret. Time	Area	eoretical Pla	Tailing Factor
Artemether+Lumefantrine Tablet (20+120)mg	lo.13ALT12401 Disso(180M	8.588	55430	11182	1.030
Artemether+Lumefantrine Tablet (20+120)mg	lo.13ALT12401 Disso(180M	8.578	53262	11091	1.013
Artemether+Lumefantrine Tablet (20+120)mg	lo.13ALT12401 Disso(180M	8.562	52551	11191	1.026
Artemether+Lumefantrine Tablet (20+120)mg	lo.13ALT12401 Disso(180M	8.558	53703	11112	1.050
Artemether+Lumefantrine Tablet (20+120)mg	lo.13ALT12401 Disso(180M	8.542	53057	10878	1.047
Artemether+Lumefantrine Tablet (20+120)mg	lo.13ALT12401 Disso(180M	8.553	52342	10903	1.049
		8.563	53391	11059	1.036
		0.197	2.084	1.234	1.490

Analysed By:

Checked By:

Name: QC 007 Serial No: 101N4112906 India Standard Time

Wave prog Friday, January 11, 2013 12:00 PM India Standard Time

Data Table

	342 nm
Lumefantrine Standard.Sample (A)	0.6784
B.No.13ALT12401,10 Min,Disso-1.Sample (A)	0.3862
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B.No.13ALT12401,10 Min,Disso-3.Sample (A)	0.3351
B.No.13ALT12401,10 Min,Disso-4.Sample (A)	0.3288
B.No.13ALT12401,10 Min,Disso-5.Sample (A)	0.3319
B.No.13ALT12401,10 Min,Disso-6.Sample (A)	0.3434
B.No.13ALT12401,15 Min,Disso-1.Sample (A)	0.4011
B.No.13ALT12401,15 Min,Disso-2.Sample (A)	0.3970
B.No.13ALT12401,15 Min,Disso-3.Sample (A)	0.4199
B.No.13ALT12401,15 Min,Disso-4.Sample (A)	0.3912
B.No.13ALT12401,15 Min,Disso-5.Sample (A)	0.3987
B.No.13ALT12401,15 Min,Disso-6.Sample (A)	0.4134
B.No.13ALT12401,30 Min,Disso-1.Sample (A)	0.5176
B.No.13ALT12401,30 Min,Disso-2.Sample (A)	0.5099
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B.No.13ALT12401,45 Min,Disso-2.Sample (A)	0.5683
B.No.13ALT12401,45 Min,Disso-3.Sample (A)	0.5685
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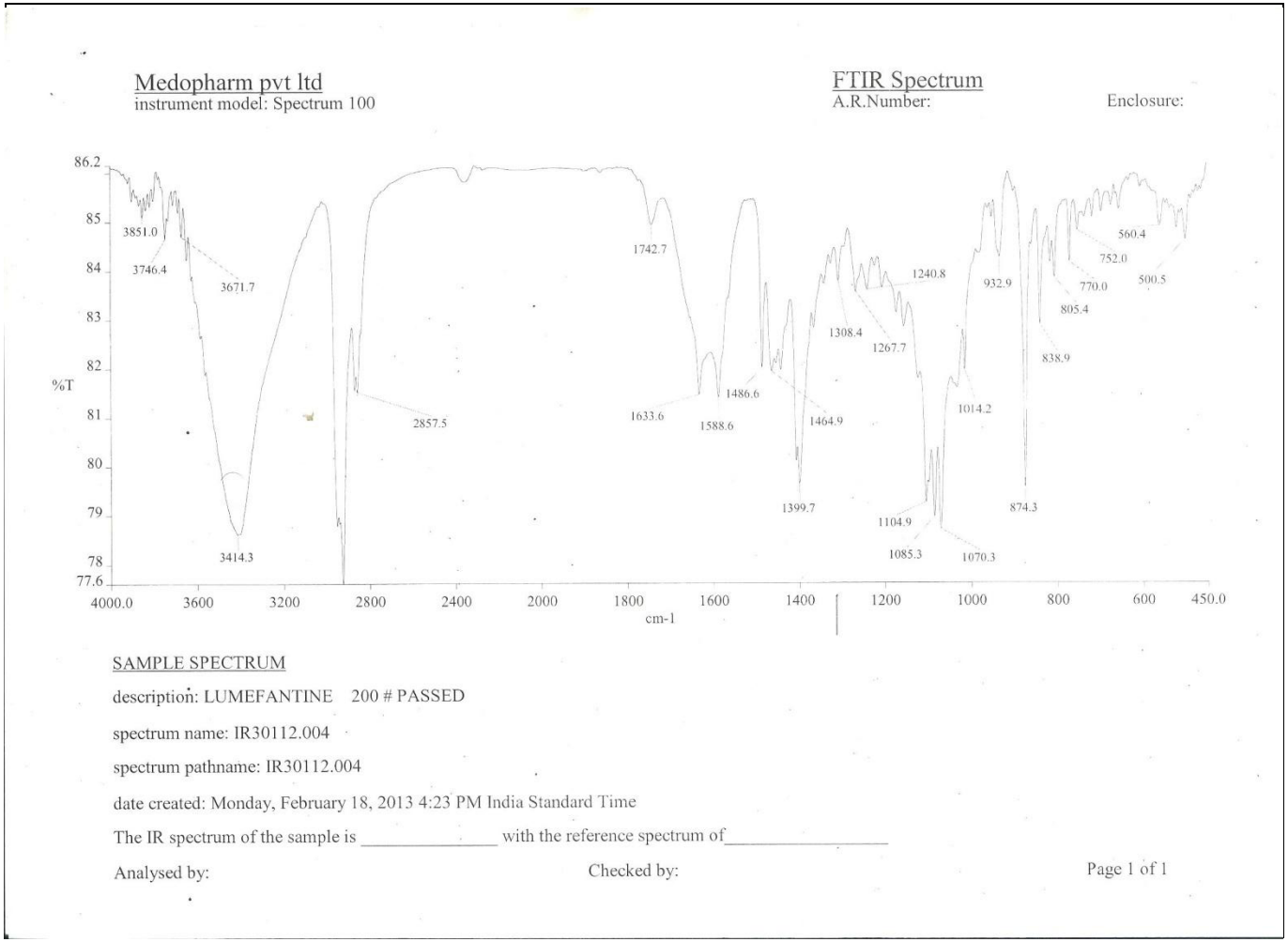
B.No.13ALT12401,45 Min,Disso-5.Sample (A)	0.5536
B.No.13ALT12401,45 Min,Disso-6.Sample (A)	0.5662
B.No.13ALT12401,60 Min,Disso-1.Sample (A)	0.6144
B.No.13ALT12401,60 Min,Disso-2.Sample (A)	0.6115
B.No.13ALT12401,60 Min,Disso-3.Sample (A)	0.6282
B.No.13ALT12401,60 Min,Disso-4.Sample (A)	0.6205
B.No.13ALT12401,60 Min,Disso-5.Sample (A)	0.6217
B.No.13ALT12401,60 Min,Disso-6.Sample (A)	0.6178

Analysed by: Checked by:

Fig.No.15


Medopharm pvt ltd
instrument model: Spectrum 100
FTIR Spectrum
A.R.Number:
Enclosure:
86.2
85
84
83
82
%T
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80
79
78
77.6
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1070.3
1014.2
932.9
874.3
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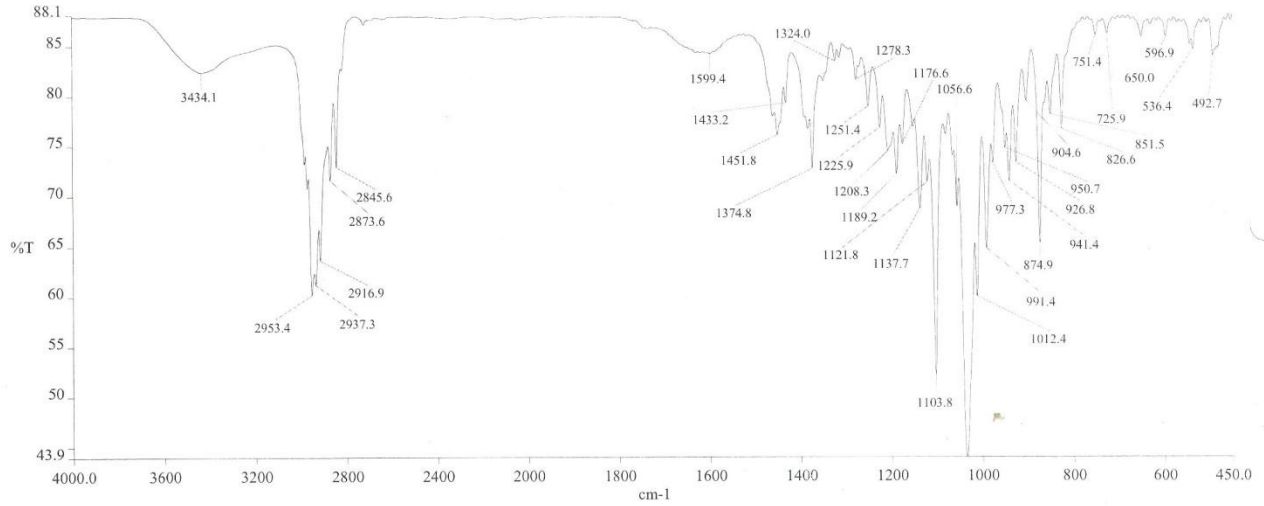
805.4
770.0
752.0
560.4
500.5
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
450.0
cm-1
SAMPLE SPECTRUM
description: LUMEFANTINE 200 # PASSED
spectrum name: IR30112.004
spectrum pathname: IR30112.004
date created: Monday, February 18, 2013 4:23 PM India Standard Time
The IR spectrum of the sample is _____ with the reference spectrum of_____
Analysed by:
Checked by:
Page 1 of 1

Fig.No.16

Medopharm pvt ltd
instrument model: Spectrum 100

FTIR Spectrum
A.R.Number:

Enclosure:



SAMPLE SPECTRUM

description: ARTEMETHER

spectrum name: IR30111.002

spectrum pathname: IR30111.002

date created: Monday, February 18, 2013 4:11 PM India Standard Time

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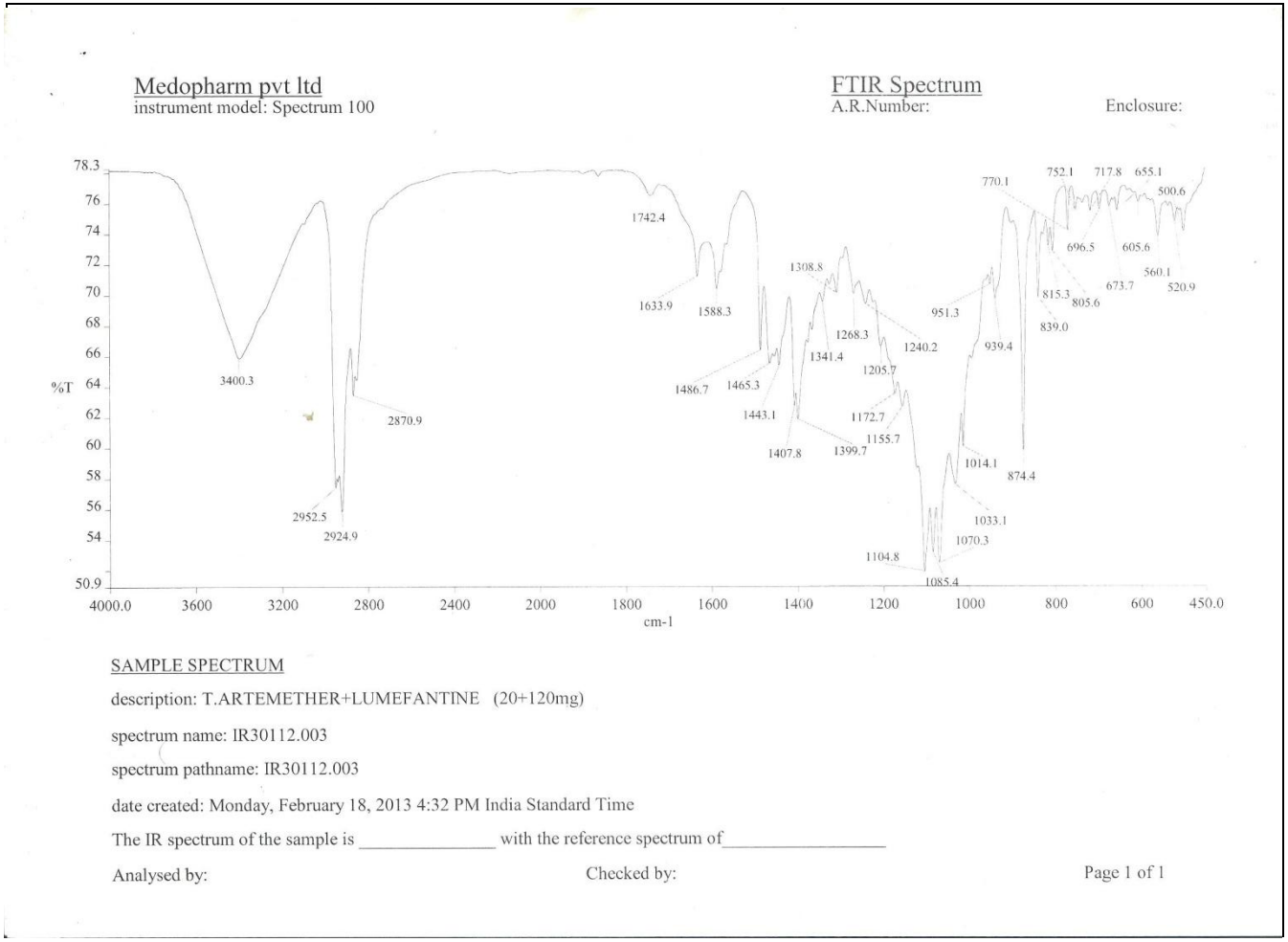
Analysed by:

Checked by:

Fig.No.17


Medopharm pvt ltd
instrument model: Spectrum 100
FTIR Spectrum
A.R.Number:
Enclosure:
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1443.1
1407.8
1399.7
1341.4
1308.8
1268.3
1240.2
1205.7
1172.7
1155.7
1104.8
1085.4
1070.3
1033.1
1014.1
951.3
939.4
874.4
839.0
815.3
805.6
770.1
752.1
717.8
696.5
673.7
655.1
605.6
560.1
520.9
500.6
SAMPLE SPECTRUM
description: T.ARTEMETHER+LUMEFANTINE (20+120mg)
spectrum name: IR30112.003
spectrum pathname: IR30112.003
date created: Monday, February 18, 2013 4:32 PM India Standard Time
The IR spectrum of the sample is _____ with the reference spectrum of_____
Analysed by:
Checked by:
Page 1 of 1

Medopharm pvt ltd
instrument model: Spectrum 100
FTIR Spectrum
A.R.Number:
Enclosure:
%T
cm-1
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2925.0
2853.6
1739.8
1602.4
1456.5
1402.7
1109.7
804.6
668.9
476.3
SAMPLE SPECTRUM
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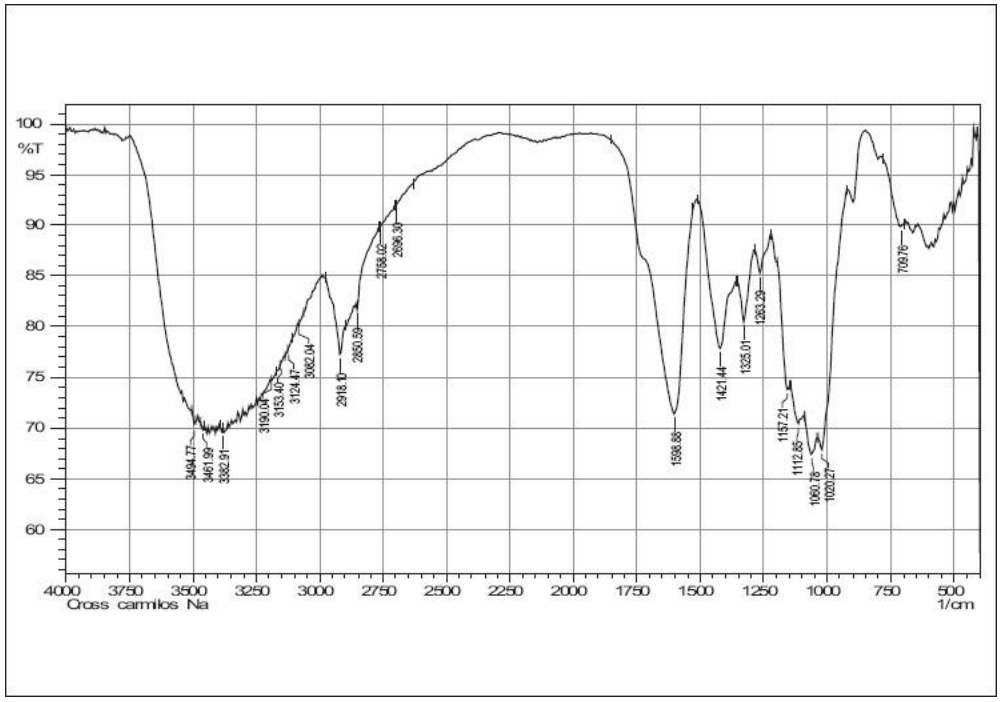
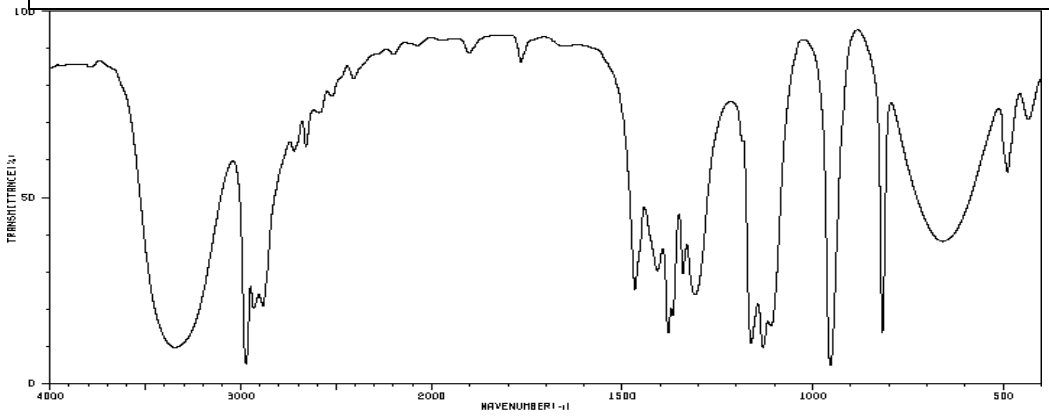
spectrum pathname: IR30110.003
date created: Monday, February 18, 2013 4:06 PM India Standard Time
The IR spectrum of the sample is _____ with the reference spectrum of _____
Analysed by:
Checked by:
Page 1 of 1

Fig.No.18

FTIR OF CCS



FTIR OF IPA



3345	9	2669	60	1467	24	1130	8	435	68	$CH_3-CH(OH)-CH_3$	
3334	9	2521	74	1409	29	1110	15				
2972	5	2408	78	1379	13	954	4				
2933	19	2307	81	1368	17	818	13				
2907	23	2198	84	1341	28	660	37				
2864	20	1903	86	1309	23	654	37				
2722	60	1766	84	1162	10	490	66				

Fig No.19

FTIR OF MCC

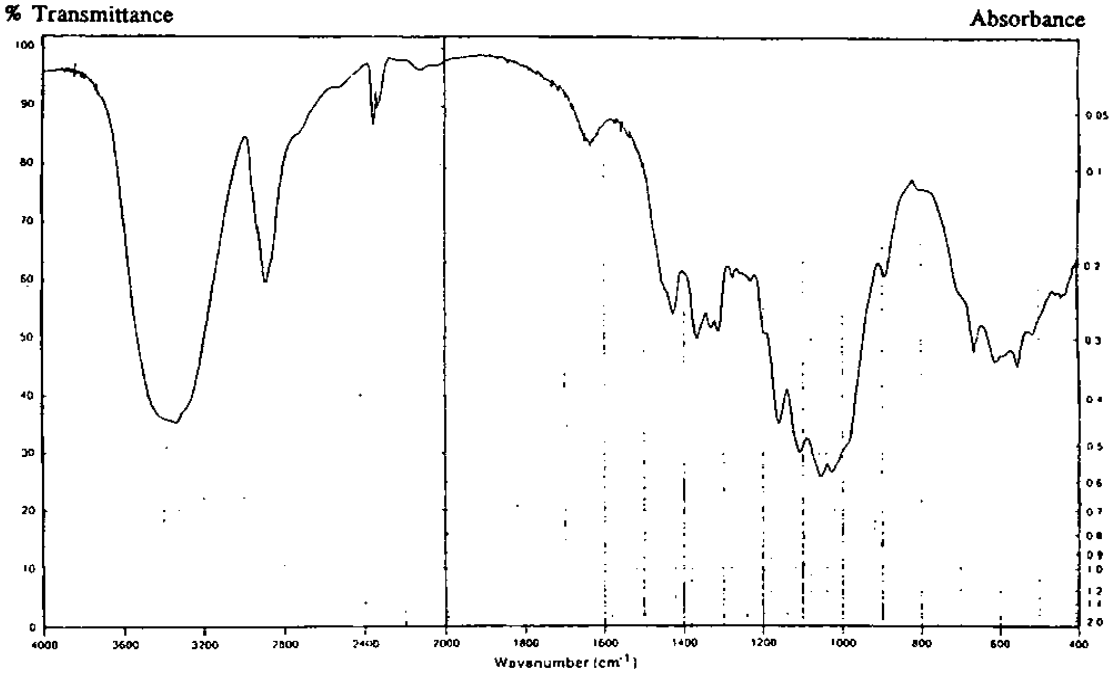


Fig No.20

STABILITY STUDY[56,57,58]

All over view

1. Purpose

Stability studies are an integral part of the drug development program and are one of the most important areas in the registration of Pharma products. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and enables recommended storage conditions, re-test periods and shelf lives to be established. Stability assessment started with studies on the substance to determine degradation products and degradation pathway. On the ICH Harmonized Tripartite Guidelines on Stability testing of New Drug substances and products, fundamental recommendations are summarized. According to the ICH guideline, long term (12 months) and accelerated stability studies (at least 6 months) have to be carried out.

2) **Storage Conditions**

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. In general cases, the study done was shown by the below Table.

Stability Study (General case):

Study	Storage condition	Minimum time period covered by Data at submission
Long term	25 ± 2°C□ and 60 ± 5 % RH or 30 ± 2°C□ and 65 ± □5 % RH	12 months
Intermediate	30 ± 2°C□ and 65 ± 5 %RH	6 months
Accelerated	40 ± 2°C and 75 ± 5 % RH	6 months

Table No.63

The stability of drug release from Artemether and Lumfantrine tablets developed in this investigation was studied under varying storage conditions. These tablets was later packed in the screw capped bottles and stored at room temperature

i) 25 ± 2°C / 60 ± 5 % RH
ii) 40 ± 2°C/ 75 ± 5% RH

All the products were stored for 3 months. After the storage period the release of Artemether and Lumefantrine from the stored product was studied. It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C□ / 60 ± 5% RH or 30 ± 2 °C□ / 65 ± □5% RH . If 30 ± □2°C□ / 65 ± 5% RH is the long-term condition, there is no intermediate condition. If long term studies are conducted at 25 ± 2°C□ / 60 ± 5% RH and significant change occurs at any time during 6 months testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.

For drug products packaged in impermeable containers (Aluminum tubes), semi permeable container (LDPE pouches, bottles etc), drug products intended for storage in a refrigerator, in a freezer and below –20°C, the study, storage condition and minimum time period covered by data at submission, are different not like as in general case.

Testing Frequency

For long term studies frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year and annually thereafter through the proposed shelf life. At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), form a 6-month study is recommended. When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points including the initial and final time points (e.g. 0, 6, 9, 12 months) form a 12 month study is recommended.

Joel Davis test

According to Joel Davis Test, if the product holds up for 3 months under accelerated condition i.e. 40°C and 75% RH (chemical stability, dissolution, physical characteristics), then in an ANDA, the generic company will be given a two year expiration date but must follow up with real time data to substantiate the dating. The method is however, also used by ethical companies in the development of new drug entities. If the product does not pass the Joel Davis test, then conventional stability testing at room temp for prolonged periods (eighteen months) must accompany the NDA or the ANDA to satisfy the stability requirements of the submission.

Generally Acceptable Design considerations for Tablets:

Tablets:

A stability study should include tests for the following characteristics of the tablet: Appearance, friability, hardness, color, odor, moisture, strength and dissolution.

.

Procedure

Artemether and Lumefanrine tablets were exposed at 40°C / 75 % RH and Normal room temperature at 30ºC / 65 % RH for 1 month.

The tablets were withdrawn for analysis of the following parameters:

- Color
- Moisture content
- Dissolution
- Assay

Stability Results of Artemether and Lumefantrine tablets (Batch No. F3) Blister pack:

Condition	Period (month)	Color	Avg. Wt (mg)	Hardness (kg / cm^2)	Moisture conent	Assay (%)
40ºC / 75% RH	1	Yellow	240	5	0.03%	99.32

Table No.64

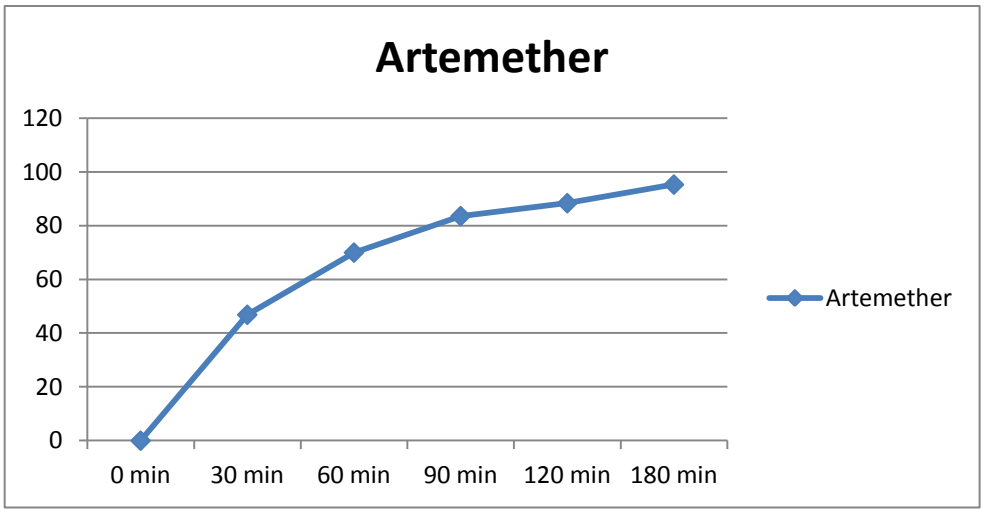
Dissolution Profile of Artemether and Lumefantrine Tablets

(Batch No.F3) Blister Pack

% Drug Release					
Time interval	30 min	60 min	90 min	120 min	180 min
Artemether	46.85	69.98	83.56	88.36	95.30
Time interval	10 min	15 min	30 min	45 min	60 min
Lumefantrine	50.86	58.67	75.91	85.76	92.04

Table No.65

Dissolution Profile Stability Batch F3 (Blister Pack)



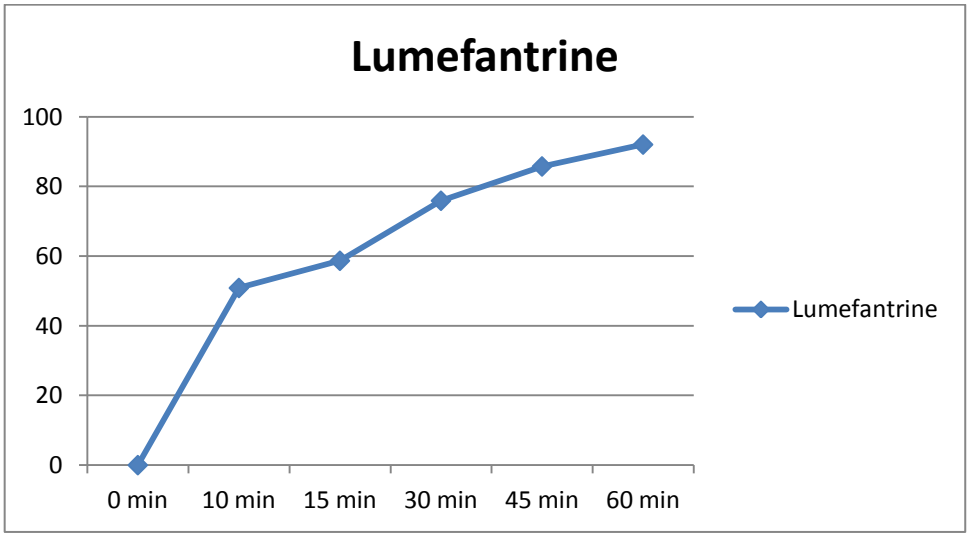


Table No.66

8.RESULTS AND DISCUSSION

Recent advances in oral drug delivery system aims to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance.

In the present research work an attempt was made to formulae oral fixed dose combination tablets using excipients of varying the concentration by wet granulation technique.

The API was subjected to preformulation study, which encompasses the "Accelerated drug excipient compatibility study", and the results obtained with selected excipients showed good compatibility with API.

In the successful tablet formulation the selected tablets were studied for their quality control test via Appearance, Thickness, Hardness, Weight variation, and Disintegration time and in- vitro dissolution study, and Assay.

From the result obtained following points can be summarized.

1. Organoleptic characteristics of pure Artemether showed that the drug is white crystalline in nature, odourless and slightly bitter in taste. Lumefanttrine showed that the drug is yellowish powder, amorphous in nature, odourless and bitter in taste (table. 26)

2. From the Compressibility index & Hausner's ratio values it is concluded that the pure drug Artemether and Lumefantrine is having very, very poor flow properties. (table.34)

3. Sieve analysis of pure Artemether shows that, all particles are not completely passed through 20# (table.30)

Sieve analysis of pure Lumefantrine shows that, all particles are not completely passed through 20# (table.31)

4. Drug-Excipients Compatibility study is initiated in order to confirm that the drug and excipent does not have any incompatibility. (table.35 & figure.15 – 20.)

5. IR spectra for drug, and powdered tablets were recorded in a Fourier transform infrared spectrophotometer with KBr pellets. From the peaks obtained, no extra peaks were seen, so all excipients are found to be compatible with API.IR spectrum of working standard is concordant with the spectrum of API (Fig.15 to17).

6. From the solubility data, It is found that Artemether and Lumefantrine is freely soluble in Dichloromethane, ethanol and insoluble in water (table 28 & 29).

7. The λ_{max} of pure drugs scanned in UV spectrometer in dissolution medium by using appropriate blank from a wavelength 200 – 400 nm shows that highest λ_{max} for Artemether – 254 nm and for Lumefantrine - 335 nm (Fig.9&10).

8. The tablet was prepared by wet granulation method by varying concentration of excipients and subjected to compression. The formulated tablets physical attributes such as percentage weight variation, Hardness, DT, Friability, Assay all of which were found to be within pharmacopieal limits (table 44).

9. Preparation of standard calibration curve in 0.1M methanolic HCL media, of both Artemether and Lumefantrine shows that highest R^2 value 0.999 (fig.7&8).

10. The results of in-vitro drug release studies in water (Artemether) and in 0.1M HCL with 1% Benzal konium chloride (Lumefantrine) are presented in (fig.11 to 14). Initially our aim was to select optimum concentration of excipients. Hence the tablets containing drug and excipients were prepared by altering the concentration of excipients.

11. The In-vitro drug release studies of these tablets shows that the cumulative drug release of Artemether in last last 180 minutes more than 98 % and of Lumefantrine in last 60 minutes is more than 90 % as compared with innovator formulation (table. 45 to 52).

12. The F3 formulation shows the similar dissolution profile i.e. the formulated tablet (F3) has higher dissolution pattern than that of the innovator tablet (coartem) (table. 50 to51)

13. By comparing the Dissimilarity (*f*1) and Similarity (*f2*) factor with that of the commercial formulation follows less dissimilar and highest similarity within given range. (table. 50 & 51)

14. Stability studies on the optimized tablet formulation at stability conditions 40 ± 2ºC and 75 ± 5 % RH, for one month (table 65 & table 66) shows good stability in Blister packing.

9. CONCLUSION

A fixed dose combination of tablet formulation of Artemether and Lumefantrine was successfully developed that has in-vitro drug release characteristics same as compared to the Conventional Coartem, Novartis Ltd., product. Moreover the developed product is morebetter with regards to formulation components and processing aspects.

Final formula of Artemether and Lumefantrine tablet

Ingredients	Batch No. F3
Lumefantrine	120.00
Artemether	20.00
Hydroxyl propyl cellulose	1.50
Polysorbate 80	3.00
Iso propyl alcohol	Qs (80 ml)
Croscarmellose sodium	5.00
Aerosil	4.00
Microcrystalline cellulose	80.50
Magnesium stearate	6.00

It is expected that this work will act as:

Benchmark for treatment of acute uncomplicated malaria caused by Plasmodium falciparum, including malaria acquired in chloroquine-resistant areas.

If the formulation technology is transferred for production of Artemether and Lumefantrine tablets in large scale then it will be cost effective in India and international market.

Utilization of total amount of drug can be improved through this fixed dose combination technique. Hence the cost of treatment can be reduced as well as patient care time.

10. REFERENCE

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